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Signed R. Mahoney

Dated 7 February 2003

Cancelled

Patents Form 1/77

Patents Act 1977
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The Patent Office

1/77

THE PATENT OFFICE
J
- 9 MAR 2002
RULE 97
NEWPORT

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — 100671

12MAR02 E702555-3 D02934
P01/7700 0.00-0205693.5

2. Patent application number
(The Patent Office will fi
0205693.5 Cancelled — 9 MAR 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
S-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)* 78224800 3

If the applicant is a corporate body, give the country/state of its incorporation — Sweden

4. Title of the invention

CHEMICAL COMPOUNDS

5. Name of your agent *(if you have one)*

Lucy Clare Padget

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG

Patents ADP number *(if you know it)* 83407620 01

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	53
Claim(s)	05
Abstract	01
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Lynda M Slack, Date
Authorised Signatory 08/03/2002

12. Name and daytime telephone number of person to contact in the United Kingdom: Lynda M Slack - 01625 - 516173

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

d) *If you have answered 'Yes' Patents Form 7/77 will need to be filed.*

e) *Once you have filled in the form you must remember to sign and date it.*

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CHEMICAL COMPOUNDS

The invention relates to pyrimidine derivatives, or pharmaceutically acceptable salts or *in vivo* hydrolysable esters thereof, which possess cell-cycle inhibitory activity and are accordingly useful for their anti-cell-proliferation (such as anti-cancer) activity and are therefore useful in methods of treatment of the human or animal body. The invention also relates to processes for the manufacture of said pyrimidine derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments of use in the production of an anti-cell-proliferation effect in a warm-blooded animal such as man.

A family of intracellular proteins called cyclins play a central role in the cell cycle. The synthesis and degradation of cyclins is tightly controlled such that their level of expression fluctuates during the cell cycle. Cyclins bind to cyclin-dependent serine/threonine kinases (CDKs) and this association is essential for CDK (such as CDK1, CDK2, CDK4 and/or CDK6) activity within the cell. Although the precise details of how each of these factors combine to regulate CDK activity is poorly understood, the balance between the two dictates whether or not the cell will progress through the cell cycle.

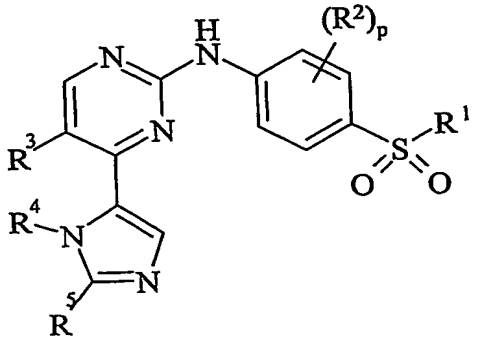
The recent convergence of oncogene and tumour suppressor gene research has identified regulation of entry into the cell cycle as a key control point of mitogenesis in tumours. Moreover, CDKs appear to be downstream of a number of oncogene signalling pathways. Disregulation of CDK activity by upregulation of cyclins and/or deletion of endogenous inhibitors appears to be an important axis between mitogenic signalling pathways and proliferation of tumour cells.

Accordingly it has been recognised that an inhibitor of cell cycle kinases, particularly inhibitors of CDK2, CDK4 and/or CDK6 (which operate at the S-phase, G1-S and G1-S phase respectively) should be of value as a selective inhibitor of cell proliferation, such as growth of mammalian cancer cells.

The present invention is based on the discovery that certain pyrimidine compounds surprisingly inhibit the effects of cell cycle kinases showing selectivity for CDK2, CDK4 and CDK6, and thus possess anti-cell-proliferation properties. Such properties are expected to be of value in the treatment of disease states associated with aberrant cell cycles and cell proliferation such as cancers (solid tumours and leukemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis; Kaposi's sarcoma, haemangioma,

acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

Accordingly, the present invention provides a compound of the formula **(IA)**, **(IB)**, **(IC)**, **(ID)**, **(IE)** and **(IF)** of the following generic structure formula **(I)**:

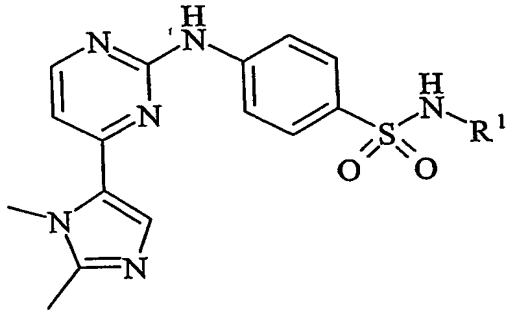


(I)

wherein R^1, R^2, R^3, R^4, R^5 and p are as defined below;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Specifically, according to the present invention there is provided a compound of formula **(IA)**:



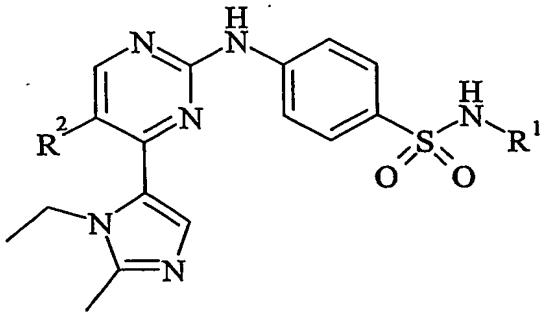
(IA)

wherein:

R^1 is 2-(pyrazolyl-1-yl)ethyl, 3-(isoxazol-3-yloxy)propyl, 2-(thiazol-3-yloxy)ethyl, 2-(thiadiazol-3-yloxy)ethyl, 1,3-dihydroxyprop-2-yl, 1-methyl-1-hydroxymethylethyl, 1,2-dimethylpropyl, 1-methylcyclopropyl, 2,2-dimethylaziridin-1-yl, *t*-butyl, 2-morpholino-1,1-dimethylethyl, 2-pyrrolidin-1-yl-1,1-dimethylethyl, 2-methylthio-1,1-dimethylethyl, 1,3-dimethoxyprop-2-yl, 1-methoxyprop-2-yl, 1-hydroxyprop-2-yl, 1-ethoxyprop-2-yl, 1-propoxyprop-2-yl, ethoxyethyl or 2-methoxy-1,1-dimethylethyl;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Accordingly, to a further aspect of the present invention there is provided a compound of formula **(IB)**:



(IB)

wherein:

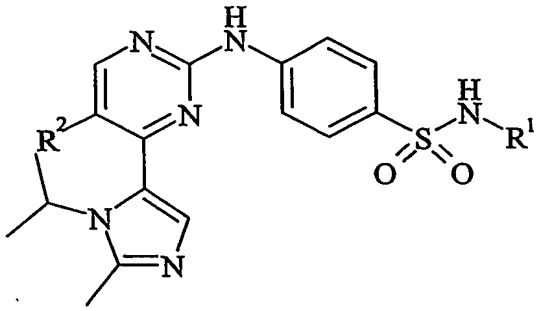
R^1 is pyrid-2-ylmethyl, 2-(2-methyl-1,2,4-triazol-5-yl)ethyl, 2-pyrid-2-ylethyl, 2-pyridazin-3-ylethyl, 2-(3,5-dimethyltriazol-4-yl)ethyl, 2-pyrid-3-ylethyl, 2-methoxyethyl, 3-(5-methylpyrazol4-yl)propyl, 2-trifluoromethylpyrid-5-ylmethyl, 2-pyridazin-4-ylethyl, 1,1-dimethylpropyn-2-yl or 2-ethoxyethyl; and

R^2 is hydrogen or cyano;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof;

provided that when R^1 is 2-methoxyethyl, R^2 is cyano.

Accordingly, to a further aspect of the present invention there is provided a compound of formula **(IC)**:



(IC)

wherein:

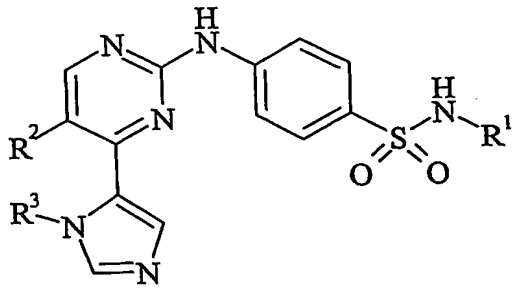
R^1 is hydrogen, C_{1-6}alkyl or C_{1-6}alkoxyC_{1-6}alkyl; and

R^2 is hydrogen, halo or cyano;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof;

provided that when R^1 is 2-methoxyethyl, R^2 is not hydrogen.

Accordingly, to a further aspect of the present invention there is provided a compound of formula **(ID)**:



(ID)

wherein:

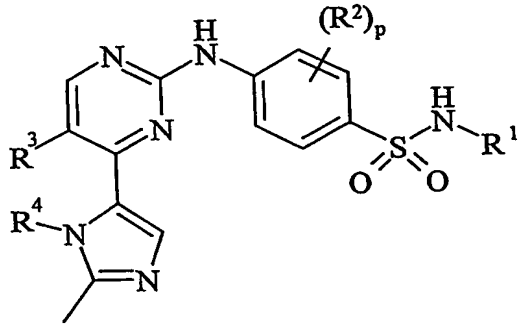
$\mathbf{R^1}$ is hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, a heterocyclyl or heterocyclylC_{1-3}alkyl; wherein R^1 may be optionally substituted on carbon by one or more methyl, ethyl, methoxy, ethoxy, propoxy, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy or cyclopropylmethoxy; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by one or more methyl, ethyl, acetyl, 2,2,2-trifluoroethyl or methoxyethyl;

$\mathbf{R^2}$ is hydrogen, halo or cyano;

$\mathbf{R^3}$ is C_{2-6}alkyl;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Accordingly, to a further aspect of the present invention there is provided a compound of formula **(IE)**:



(IE)

wherein:

$\mathbf{R^1}$ is hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, a heterocyclyl or heterocyclylC_{1-3}alkyl; wherein R^1 may be optionally substituted on carbon by one or more methyl, ethyl, methoxy, ethoxy, propoxy,

trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy or cyclopropylmethoxy; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by one or more methyl, ethyl, acetyl, 2,2,2-trifluoroethyl or methoxyethyl;

R^2 is halo, cyano, C_{1-3}alkyl or C_{1-3}alkoxy;

p is 1-2; wherein the values of R^2 may be the same or different;

R^3 is hydrogen, halo or cyano;

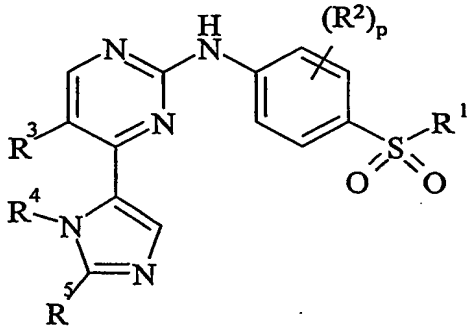
R^4 is C_{1-4}alkyl;

R^5 is C_{1-6}alkyl or C_{2-6}alkenyl; wherein R^5 may be optionally substituted on carbon by one or more methoxy, ethoxy, propoxy, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy or cyclopropylmethoxy;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof;

provided that said compound is not 4-(1,2-dimethylimidazol-5-yl)-2-[2-methoxy-4-(*N*-methylsulphamoyl)-5-methylanilino]pyrimidine.

Accordingly, to a further aspect of the present invention there is provided a compound of formula (IF):



(IF)

wherein:

R^1 is C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, a heterocyclyl or heterocyclylC_{1-3}alkyl; wherein R^1 may be optionally substituted on carbon by one or more methyl, ethyl, methoxy, ethoxy, propoxy, trifluoromethyl, trifluoromethoxy, dimethylamino, 2,2,2-trifluoroethoxy or cyclopropylmethoxy; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by one or more methyl, ethyl, acetyl, 2,2,2-trifluoroethyl or methoxyethyl;

R^2 is halo, cyano, C_{1-3}alkyl or C_{1-3}alkoxy;

p is 0-2; wherein the values of R^2 may be the same or different;

R^3 is hydrogen, halo or cyano;

R^4 is C_{2-6}alkyl;

R^5 is C_{1-6}alkyl or C_{2-6}alkenyl; wherein R^5 may be optionally substituted on carbon by one or more methoxy, ethoxy, propoxy, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy or cyclopropylmethoxy;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. For example, "C_{1-6}alkyl","C_{2-6}alkyl", "C_{1-4}alkyl" and "C_{1-3}alkyl" include ethyl, propyl and isopropyl. However, references to individual alkyl groups such as 'propyl' are specific for the straight chained version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only. A similar convention applies to other radicals, for example "C_{3-6}cycloalkylC_{1-3}alkyl" includes cyclopropylmethyl, 1-cyclobutylethyl and 2-cyclopentylethyl. The term "halo" refers to fluoro, chloro, bromo and iodo.

Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

A "heterocyclyl" is a saturated, partially saturated or unsaturated, monocyclic ring containing 4-6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, and a ring sulphur atom may be optionally oxidised to form the S-oxide(s). Examples and suitable values of the term "heterocyclyl" are morpholino, piperidyl, pyridyl, pyranyl, pyrrolyl, isothiazolyl, thienyl, thiadiazolyl, piperazinyl, thiazolidinyl, thiomorpholino, pyrrolinyl, tetrahydropyranyl, tetrahydrofuryl, imidazolyl, pyrimidyl, pyrazinyl, pyridazinyl and isoxazolyl. Suitably a "heterocyclyl" is tetrahydrofuryl.

Examples of "C_{1-3}alkoxy" include methoxy, ethoxy and propoxy. Examples of "C_{2-6}alkenyl" and "C_{2-4}alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C_{2-4}alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of "C_{3-6}cycloalkyl" are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Examples of "heterocyclylC_{1-3}alkyl" include pyridylmethyl, 3-morpholinopropyl and 2-pyrimid-2-ylethyl. Examples of "C_{1-6}alkoxyC_{1-6}alkyl" are methoxyethyl, 2-ethoxymethyl, 2-ethoxypropyl and 2-ethoxyethyl.

A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for

example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

An *in vivo* hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring.

Some compounds of the formula (I) may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers that possess CDK inhibitory activity.

The invention relates to any and all tautomeric forms of the compounds of the formula (I) that possess CDK inhibitory activity. In particular the skilled reader will appreciate that when R^4 is hydrogen, the imidazole ring as drawn in formula (I) may tautomerise.

It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess CDK inhibitory activity.

Suitable values of R^1, R^2, R^3, R^4, R^5 and p are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

For compounds of formula (IC).

R^1 is hydrogen or C_{1-6}alkoxyC_{1-6}alkyl.

R^1 is methyl, methoxyethyl or ethoxyethyl.

R^2 is hydrogen or halo.

R^2 is hydrogen or bromo.

For compounds of formula (ID).

R^1 is C_{1-4}alkyl, C_{3-6}cycloalkyl or heterocyclylC_{1-3}alkyl; wherein R^1 may be optionally substituted on carbon by one methoxy.

R^1 is cyclopropyl, 2-methoxyethyl or tetrahydrofur-2-ylmethyl.

R^2 is hydrogen.

R^3 is ethyl or isopropyl.

For compounds of formula (IE).

R^1 is hydrogen or C_{1-4}alkyl; wherein R^1 may be optionally substituted on carbon by one methoxy.

R^1 is hydrogen or 2-methoxyethyl.

R^2 is halo.

R^2 is fluoro.

p is 1.

R^3 is hydrogen.

R^4 is methyl.

For compounds of formula (IF).

R^1 is C_{1-4}alkyl; wherein R^1 may be optionally substituted on carbon by one or more methoxy, trifluoromethyl or dimethylamino.

R^1 is methyl, 3-dimethylaminopropyl, 3-methoxypropyl, 3,3,3-trifluoropropyl or butyl.

p is 0.

R^3 is hydrogen.

R^4 is isopropyl.

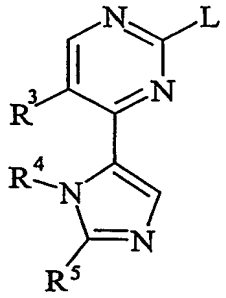
R^5 is methyl.

In another aspect of the invention, particular compounds of the invention are any one of the Examples or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

A particular aspect of the invention is that which relates to the compound of formula **(I)** or a pharmaceutically acceptable salt thereof.

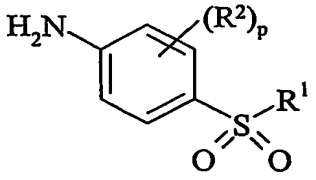
Another aspect of the present invention provides a process for preparing a compound of formula **(I)** or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof which process (wherein R^1, R^2, R^3, R^4, R^5, R^6, n, p and q are, unless otherwise specified, as defined in formula **(I)**) comprises of:

Process a) reaction of a pyrimidine of formula **(II)**:



(II)

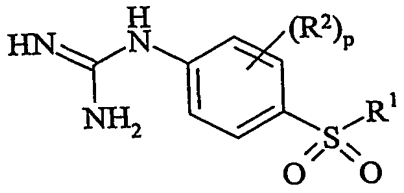
wherein L is a displaceable group; with an aniline of formula **(III)**:



(III)

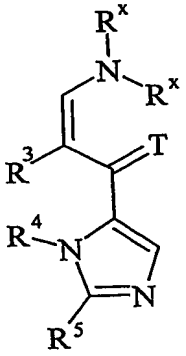
or

Process b) reacting a compound of formula **(IV)**:



(IV)

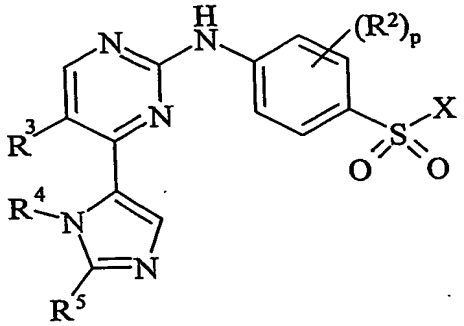
with a compound of formula (V):



(V)

wherein T is O or S; R^x may be the same or different and is C_{1-6}alkyl;

Process c) for compounds of formula (I) where R^1 is amino or a group R^1-NH_2-; reacting a pyrimidine of formula (VI):



(VI)

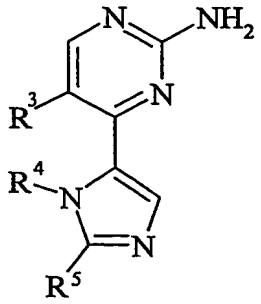
wherein X is a displaceable group; with an amine of formula (VII):

R^a-NH_2

(VII)

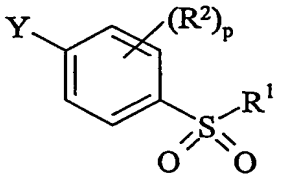
wherein R^a is hydrogen or R^1;

Process d) reacting a pyrimidine of formula (VIII)



(VIII)

with a compound of formula (IX):



(IX)

where Y is a displaceable group;

and thereafter if necessary:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

L is a displaceable group, suitable values for L are for example, a halogeno or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group.

X is a displaceable group, suitable values for X are for example, a fluoro or chloro group. Preferably X is fluoro.

Y is a displaceable group, suitable values for Y are for example, a halogeno or sulphonyloxy group, for example a bromo, iodo or trifluoromethanesulphonyloxy group. Preferably Y is iodo.

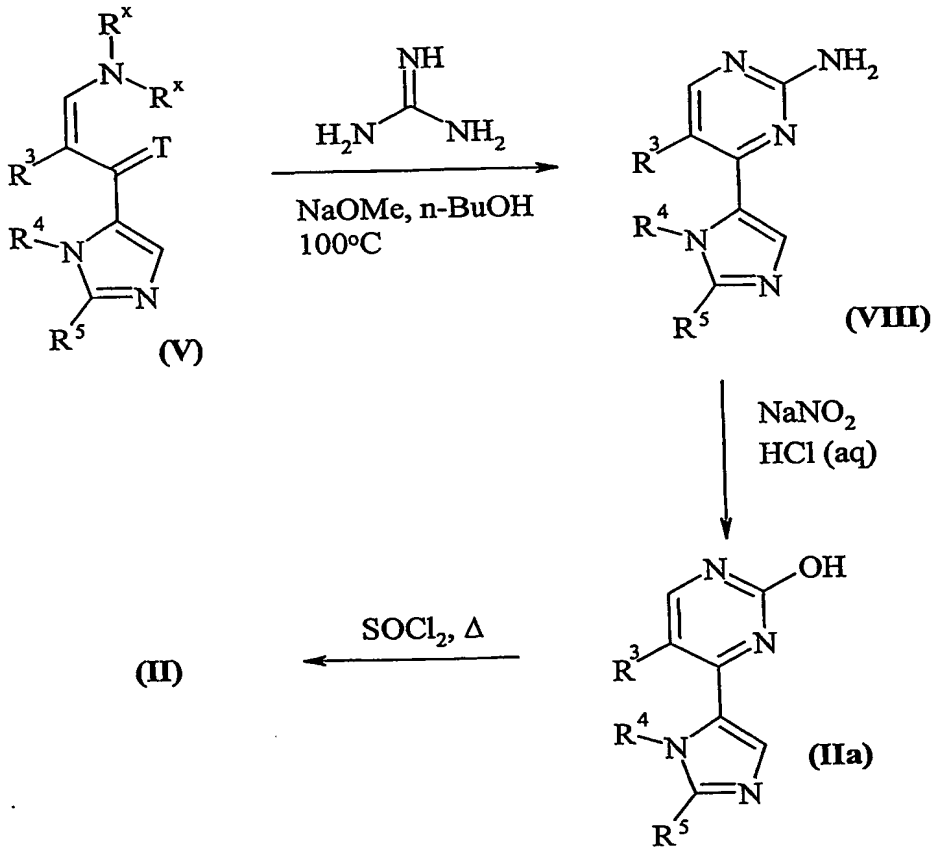
Specific reaction conditions for the above reactions are as follows.

Process a) Pyrimidines of formula (II) and anilines of formula (III) may be reacted together:

i) in the presence of a suitable solvent for example a ketone such as acetone or an alcohol such as ethanol or butanol or an aromatic hydrocarbon such as toluene or *N*-methyl pyrrolidine, optionally in the presence of a suitable acid for example an inorganic acid such as

hydrochloric acid or sulphuric acid, or an organic acid such as acetic acid or formic acid (or a suitable Lewis acid) and at a temperature in the range of 0°C to reflux, preferably reflux; or ii) under standard Buchwald conditions (for example see *J. Am. Chem. Soc.*, **118**, 7215; *J. Am. Chem. Soc.*, **119**, 8451; *J. Org. Chem.*, **62**, 1568 and 6066) for example in the presence of palladium acetate, in a suitable solvent for example an aromatic solvent such as toluene, benzene or xylene, with a suitable base for example an inorganic base such as caesium carbonate or an organic base such as potassium-*t*-butoxide, in the presence of a suitable ligand such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and at a temperature in the range of 25 to 80°C.

Pyrimidines of the formula **(II)** where L is chloro may be prepared according to *Scheme 1*:



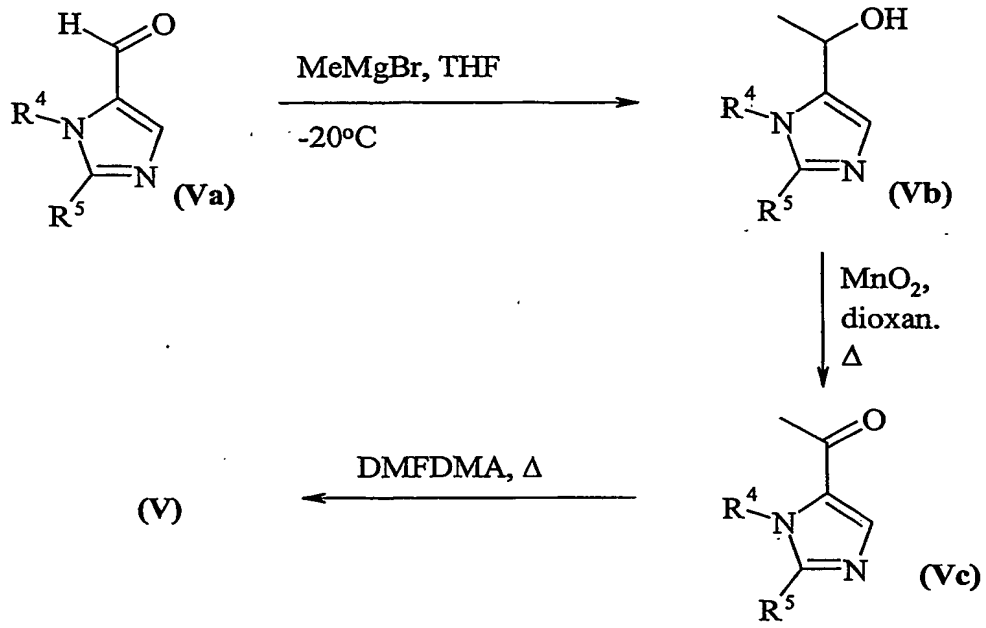
Scheme 1

Anilines of formula **(III)** are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process b) Compounds of formula **(IV)** and compounds of formula **(V)** are reacted together in a suitable solvent such as *N*-methylpyrrolidinone or butanol at a temperature in the

range of 100-200°C, preferably in the range of 150-170°C. The reaction is preferably conducted in the presence of a suitable base such as, for example, sodium hydride, sodium methoxide or potassium carbonate.

Compounds of formula **(V)** may be prepared according to *Scheme 2*:

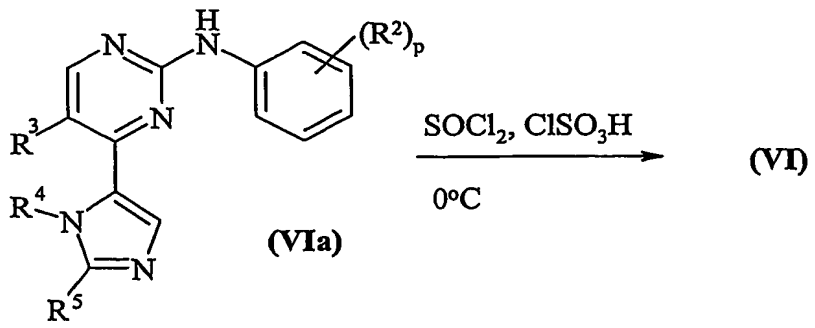


Scheme 2

Compounds of formula **(IV)** and **(Va)** are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process c) Compounds of formula **(VI)** and amines of formula **(VII)** may be reacted together in the presence of an inert solvent such as *N*-methylpyrrolidinone or pyridine, in the presence of a base for example an inorganic base such as caesium carbonate or in the presence of an organic base such as excess **(VII)** and at a temperature in the range of 25 to 80°C.

Compounds of formula **(VI)** (wherein X is chloro) may be prepared according to *Scheme 3*:



Scheme 3

Compounds of formula **(VIa)** may be prepared according to *Process a*, *Process b* or *Process d* wherein q is 0.

Process d) Compounds of formula **(VIII)** and amines of formula **(IX)** may be reacted together under standard Buchwald conditions as described in *Process a*.

The synthesis of compounds of formula **(VIII)** is described in *Scheme 1*.

Compounds of formula **(IX)** are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Amines of formula **(VI)** are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

As stated hereinbefore the compounds defined in the present invention possesses anti-cell-proliferation activity such as anti-cancer activity which is believed to arise from the

CDK inhibitory activity of the compound. These properties may be assessed, for example, using the procedures set out in WO 02/04429.

Although the pharmacological properties of the compounds of the formula (I) vary with structural change, in general activity possessed by compounds of the formula (I) may be demonstrated at IC_{50} concentrations or doses in the range 250μM to 1nM in the in vitro assay described in WO 02/04429.

Typical IC_{50} values for compounds of the invention when tested in the SRB assay described in WO 02/04429 are in the range 1mM to 1nM.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a pyrimidine derivative of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compound of formula (I) will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.1-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

According to a further aspect of the present invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, are effective cell cycle inhibitors (anti-cell proliferation agents), which property is believed to arise from their CDK

inhibitory properties. Accordingly the compounds of the present invention are expected to be useful in the treatment of diseases or medical conditions mediated alone or in part by CDK enzymes, i.e. the compounds may be used to produce a CDK inhibitory effect in a warm-blooded animal in need of such treatment. Thus the compounds of the present invention provide a method for treating the proliferation of malignant cells characterised by inhibition of CDK enzymes, i.e. the compounds may be used to produce an anti-proliferative effect mediated alone or in part by the inhibition of CDKs. Such a compound of the invention is expected to possess a wide range of anti-cancer properties as CDKs have been implicated in many common human cancers such as leukaemia and breast, lung, colon, rectal, stomach, prostate, bladder, pancreas and ovarian cancer. Thus it is expected that a compound of the invention will possess anti-cancer activity against these cancers. It is in addition expected that a compound of the present invention will possess activity against a range of leukaemias, lymphoid malignancies and solid tumours such as carcinomas and sarcomas in tissues such as the liver, kidney, prostate and pancreas. In particular such compounds of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin. More particularly such compounds of the invention, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with CDKs, especially those tumours which are significantly dependent on CDKs for their growth and spread, including for example, certain tumours of the colon, breast, prostate, lung, vulva and skin.

It is further expected that a compound of the present invention will possess activity against other cell-proliferation diseases in a wide range of other disease states including leukaemias, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

Thus according to this aspect of the invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore for use as a medicament; and the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal such as man. Particularly,

an inhibitory effect is produced by preventing entry into or progression through the S phase by inhibition of CDK2, CDK4 and/or CDK6, especially CDK2.

According to a further feature of the invention, there is provided a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before in the manufacture of a medicament for use in the treatment of cancers (solid tumours and leukaemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation, particularly in the treatment of cancers.

According to a further feature of this aspect of the invention there is provided a method for producing a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound as defined immediately above. Particularly, an inhibitory effect is produced by preventing entry into or progression through the S phase by inhibition of CDK2, CDK4 and/or CDK6, especially CDK2.

According to a further feature of this aspect of the invention there is provided a method for producing a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof as defined herein before. Particularly, an inhibitory effect is produced by preventing entry into or progression through the S phase by inhibition of CDK2, CDK4 and/or CDK6, especially CDK2.

According to an additional feature of this aspect of the invention there is provided a method of treating cancers (solid tumours and leukaemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof as defined herein before.

Particularly there is provided a method of treating cancer in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an

effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof as defined herein before.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or carrier for use in the production of a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal such as man.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of cancers (solid tumours and leukaemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation, in a warm-blooded animal such as man.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of cancer in a warm-blooded animal such as man.

Preventing cells from entering DNA synthesis by inhibition of essential S-phase initiating activities such as CDK2 initiation may also be useful in protecting normal cells of the body from toxicity of cycle-specific pharmaceutical agents. Inhibition of CDK2 or 4 will prevent progression into the cell cycle in normal cells which could limit the toxicity of cycle-specific pharmaceutical agents which act in S-phase, G2 or mitosis. Such protection may result in the prevention of hair loss normally associated with these agents.

Therefore in a further aspect of the invention there is provided a compound of formula (I) as defined above or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof for use as a cell protective agent.

Therefore in a further aspect of the invention there is provided a compound of formula (I) as defined above or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof

for use in preventing hair loss arising from the treatment of malignant conditions with pharmaceutical agents.

Examples of pharmaceutical agents for treating malignant conditions that are known to cause hair loss include alkylating agents such as ifosfamide and cyclophosphamide; antimetabolites such as methotrexate, 5-fluorouracil, gemcitabine and cytarabine; vinca alkaloids and analogues such as vincristine, vinbalstine, vindesine, vinorelbine; taxanes such as paclitaxel and docetaxel; topoisomerase I inhibitors such as irintotecan and topotecan; cytotoxic antibiotics such as doxorubicin, daunorubicin, mitoxantrone, actinomycin-D and mitomycin; and others such as etoposide and tretinoin.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, may be administered in association with a one or more of the above pharmaceutical agents. In this instance the compound of formula (I) may be administered by systemic or non systemic means. Particularly the compound of formula (I) my may administered by non-systemic means, for example topical administration.

Therefore in an additional feature of the invention, there is provided a method of preventing hair loss during treatment for one or more malignant conditions with pharmaceutical agents, in a warm-blooded animal, such as man, which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

In an additional feature of the invention, there is provided a method of preventing hair loss during treatment for one or more malignant conditions with pharmaceutical agents, in a warm-blooded animal, such as man, which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof in simultaneous, sequential or separate administration with an effective amount of said pharmaceutical agent.

According to a further aspect of the invention there is provided a pharmaceutical composition for use in preventing hair loss arising from the treatment of malignant conditions with pharmaceutical agents which comprises a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, and said pharmaceutical agent, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo*

hydrolysable ester thereof, and a pharmaceutical agent for treating malignant conditions that is known to cause hair loss.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, in a first unit dosage form;

b) a pharmaceutical agent for treating malignant conditions that is known to cause hair loss; in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, in the manufacture of a medicament for the prevention of hair loss during treatment of malignant conditions with pharmaceutical agents.

According to a further aspect of the present invention there is provided a combination treatment for the prevention of hair loss comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of a pharmaceutical agent for treatment of malignant conditions to a warm-blooded animal, such as man.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular cell-proliferation disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 1-100 mg/kg, preferably 1-50 mg/kg is envisaged.

The CDK inhibitory activity defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the cell cycle inhibitory treatment defined hereinbefore may be: surgery, radiotherapy or chemotherapy. Such chemotherapy may cover three main categories of therapeutic agent:

(i) other cell cycle inhibitory agents that work by the same or different mechanisms from those defined hereinbefore;

(ii) cytostatic agents such as antioestrogens (for example tamoxifen,toremifene, raloxifene, droloxifene, iodoxyfene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrazole, vorazole, exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, luprolide), inhibitors of testosterone 5α-dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors); and

(iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); antimitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan). According to this aspect of the invention there is provided a pharmaceutical product comprising a compound of the formula (I) as defined hereinbefore and an additional anti-tumour substance as defined hereinbefore for the conjoint treatment of cancer.

In addition to their use in therapeutic medicine, the compounds of formula (I) and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of in vitro and *in vivo* test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Examples

The invention will now be illustrated by the following non limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30mmHg) with a bath temperature of up to 60°C;

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectral data;

(vi) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio dimethyl sulphoxide (DMSO-d_6) as solvent unless otherwise indicated;

(viii) chemical symbols have their usual meanings; SI units and symbols are used;

(ix) solvent ratios are given in volume:volume (v/v) terms; and

(x) mass spectra were run with an electron energy of 70 electron volts in the chemical ionization (CI) mode using a direct exposure probe; where indicated ionization was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z are given; generally, only ions which indicate the parent mass are reported; and unless otherwise stated, the mass ion quoted is $(MH)^+$;

(xi) unless stated otherwise compounds containing an asymmetrically substituted carbon and/or sulphur atom have not been resolved;

(xii) where a synthesis is described as being analogous to that described in a previous example the amounts used are the millimolar ratio equivalents to those used in the previous example;

(xvi) the following abbreviations have been used:

DMFDMA	dimethylformamide dimethylacetal;
DMF	dimethylformamide;
EtOAc	ethyl acetate;
ether	diethyl ether;
MeOH	methanol; and
DCM	dichloromethane;

xvii) where an Isolute SCX-2 column is referred to, this means an "ion exchange" extraction cartridge for adsorption of basic compounds, i.e. a polypropylene tube containing a benzenesulphonic acid based strong cation exchange sorbent, used according to the manufacturers instructions obtained from International Sorbent Technologies Limited, Dyffryn Business Park, Hengeod, Mid Glamorgan, UK, CF82 7RJ;

xviii) where an Isolute amine column is referred to, this means an "ion exchange" extraction cartridge for adsorption of acidic compounds, i.e. a polypropylene tube containing a amino silane covalently bonded to a silica particle used according to the manufacturers instructions obtained from International Sorbent Technologies Limited, Dyffryn Business Park, Hengeod, Mid Glamorgan, UK, CF82 7RJ; and

xix) where a Chemelut column is referred to, this means an extraction cartridge for removal of water, i.e. a polypropylene tube containing diatomaceous earth used according to the manufacturers instructions obtained from Varian, Harbor City, California, USA.

Example 1

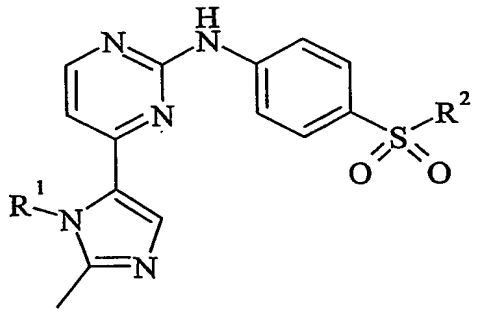
4-(1-Ethyl-2-methylimidazol-5-yl)-2-{4-[*N*-(2-ethoxyethyl)sulphamoyl]anilino}pyrimidine

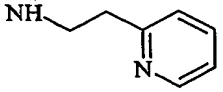
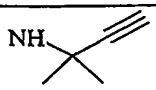
Chlorosulphonic acid (280µl, 4mmol) was added dropwise to solution of 2-anilino-4-(1-ethyl-2-methylimidazol-5-yl)pyrimidine (Method 17; 279mg, 1mmol) in thionyl chloride (5ml) cooled at 0°C and the mixture stirred at 0°C for 10 minutes then heated at 90°C for 90 minutes. The volatiles were removed by evaporation and the residue was dried under high vacuum (<2mmHg) for 1 hour. The resulting solid was placed under nitrogen and a solution of 2-ethoxyethylamine (356mg, 4mmol) and diethylmethylamine (1ml, 15mmol) in MeOH (3ml) added. The mixture was stirred for 15 minutes and the volatiles were evaporated in

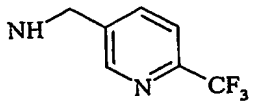
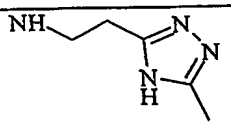
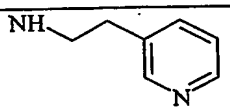
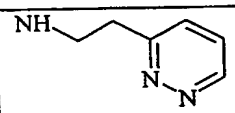
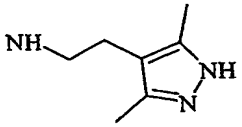
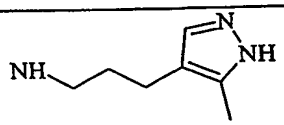
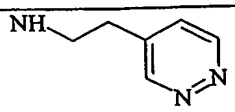
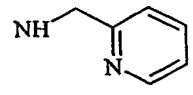
vacuo. Water (20ml) was added and extracted DCM (2 x 25ml). DCM was dried and evaporated in vacuo. The residue was purified by flash chromatography on silica gel eluting with DCM:MeOH (100:0 increasing in polarity to 97:3) to yield a white foam. The white foam was dissolved in MeOH (3ml) and treated with 1M HCl in ether (0.55ml, 0.55mmol). The solvent was evaporated in vacuo and the resultant solid triturated with ether, collected by filtration and dried under vacuum at 60°C to yield the title compound (128mg, 47%) as a yellow solid. NMR: 1.05 (t, 3H), 1.30 (t, 3H), 2.76 (s, 3H), 2.88 (m, 2H), 3.32 (m, 4H), 4.76 (m, 2H), 7.37 (d, 1H), 7.52 (m, 1H), 7.73 (d, 2H), 7.90 (d, 2H), 8.43 (s, 1H), 8.65 (d, 1H), 10.14 (brs, 1H); m/z 431.

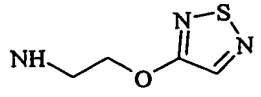
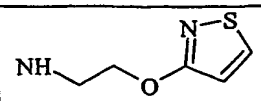
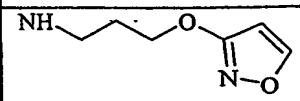
Examples 2-14

The following compounds were prepared by the procedure of Example 1 using the appropriate amine and 2-anilino-4-(1-ethyl-2-methylimidazol-5-yl)pyrimidine (Method 17; Examples 2-11) and 2-anilino-4-(1,2-dimethylimidazol-5-yl)pyrimidine (Method 21; Examples 12-14).



Ex	R^1	R^2	NMR	M/z
2 [2]	Et		1.28 (t, 3H), 2.72 (s, 3H), 3.18 (m, 2H), 3.22 (m, 2H), 4.74 (q, 2H), 7.38 (d, 1H), 7.70 (d, 2H), 7.78 (t, 1H), 7.88 (t, 4H), 8.42 (t, 1H), 8.47 (s, 1H), 8.68 (d, 1H), 8.78 (d, 1H), 10.19 (s, 1H),	464
3 [3]	Et		1.28 (t, 3H), 1.40 (s, 6H), 2.71 (s, 3H), 2.91 (s, 1H), 4.72 (q, 2H), 7.34 (d, 1H), 7.74 (d, 2H), 7.83 (d+m, 3H), 8.43 (s, 1H), 8.68 (d, 1H), 10.11 (s, 1H),	425

4 [4]	Et		1.30 (t, 3H), 2.75 (s, 3H), 4.18 (d, 2H), 5.78 (q, 2H), 7.40 (d, 1H), 7.72 (d, 2H), 7.80 (d, 1H), 7.88 (d, 2H), 7.94 (d, 1H), 8.29 (t, 1H), 8.48 (s, 1H), 8.60 (s, 1H), 8.70 (d, 1H), 10.18 (s, 1H),	518
5 [5]	Et		1.25 (t, 3H), 2.49 (s, 3H), 2.72 (s, 3H), 2.95 (m, 2H), 3.16 (m, 2H), 4.73 (q, 2H), 7.39 (d, 1H), 7.75 (d, 2H), 7.78 (m, 1H), 7.90 (d, 2H), 8.48 (s, 1H), 8.67 (d, 1H), 10.20 (s, 1H),	468
6 [5]	Et		1.25 (t, 3H), 2.70 (s, 3H), 2.82 (m, 2H), 3.04 (m, 2H), 4.72 (q, 2H), 7.38 (d, 1H), 7.63 (m, 2H), 7.70 (d, 2H), 7.88 (d, 2H), 8.01 (d, 1H), 8.41 (s, 1H), 8.60 (m, 2H), 8.65 (d, 1H), 10.15 (s, 1H),	464
7 [6, 14]	Et		1.25 (t, 3H), 2.70 (s, 3H), 3.08 (t, 2H), 3.18 (q, 2H), 4.72 (q, 2H), 7.38 (d, 1H), 7.68 (t, 1H), 7.70 (m, 4H), 7.88 (d, 2H), 8.48 (s, 1H), 8.68 (d, 1H), 9.15 (d, 1H), 10.18 (s, 1H)	465
8 [7]	Et		1.24 (t, 3H), 2.22 (s, 6H), 2.50 (m, 2H), 2.71 (s, 3H), 2.82 (m, 2H), 4.72 (q, 2H), 7.39 (d, 1H), 7.60 (t, 1H), 7.71 (d, 2H), 7.89 (d, 2H), 8.47 (s, 1H), 8.68 (d, 1H), 10.18 (s, 1H),	481
9 [8]	Et		1.25 (t, 3H), 1.54 (m, 2H), 2.14 (s, 3H), 2.34 (t, 2H), 2.72 (m, 5H), 4.72 (q, 2H), 7.36 (d, 1H), 7.47 (t, 1H), 7.59 (s, 1H), 7.71 (d, 2H), 7.88 (d, 2H), 8.43 (s, 1H), 8.67 (d, 1H), 10.12 (s, 1H),	481
10 [9]	Et		1.25 (t, 3H), 2.70 (m, 5H), 2.81 (t, 2H), 3.08 (m, 2H), 4.72 (q, 2H), 7.37 (d, 1H), 7.64 (m 1H), 7.71 (d+s, 3H), 7.89 (d, 2H), 8.45 (s, 1H), 8.68 (d, 1H), 9.19 (d, 2H), 10.14 (s, 1H),	465
11	Et		1.20 (t, 3H), 2. 38 (s, 3H), 4.04 (s, 2H), 4.58 (q, 2H), 7.21 (m, 2H), 7.37 (d, 1H), 7.70 (m, 4H), 7.84 (d, 2H), 8.41 (d, 2H), 9.80 (s, 1H)	450

12 [10, 12]	Me		2.35 (s, 3H), 3.20 (t, 2H), 3.95 (s, 3H), 4.35 (t, 2H), 7.20 (d, 1H), 7.65 (s, 1H), 7.75 (m, 3H), 7.93 (d, 2H), 8.30 (s, 1H), 8.45 (d, 1H), 9.95 (s, 1H)	473
13 [11]	Me		2.35 (s, 3H), 3.12 (m, 2H), 3.95 (s, 3H), 4.25 (t, 2H), 6.65 (d, 1H), 7.2 (d, 1H), 7.60 (s, 1H), 7.7 (m, 3H), 7.9 (d, 2H), 8.25 (d, 1H), 8.82 (d, 1H), 9.9 (s, 1H)	472
14 [10, 13]	Me		1.84 (m, 2H), 2.40 (s, 3H), 2.90 (t, 2H), 3.95 (s, 3H), 4.20 (t, 2H), 6.25 (s, 1H), 7.25 (d, 1H), 7.50 (brs, 1H), 7.65 (s, 1H), 7.75 (d, 2H), 7.95 (d, 2H), 8.45 (d, 1H), 8.65 (s, 1H), 9.95 (s, 1H)	468 $(M-H)^-$

[1] Isolated as Free Base

[2] Purified by flash silica chromatography DCM:MeOH (96:4)

[3] Purified by flash silica chromatography DCM:MeOH (98:2 increasing in polarity to 96:4)

[4] Purified by flash silica chromatography DCM:MeOH (95:5)

[5] Purified by flash silica chromatography DCM:MeOH (98:2 increasing in polarity to 90:10). The residue was further purified by flash alumina chromatography DCM:MeOH (90:10)

[6] Water (15ml) added, basified with saturated sodium bicarbonate solution to pH 8, extracted into ethyl acetate (5 x 15ml). Organics were washed with brine (10ml), dried evaporated.[7] Purified by flash alumina chromatography DCM:MeOH (96:4 increasing in polarity to 80:20).

[8] Purified by flash alumina chromatography DCM:MeOH (98:2 increasing in polarity to 90:10).

[9] Purified by flash alumina chromatography DCM:MeOH (96:4 increasing in polarity to 90:10). The residue was further purified by flash silica chromatography (DCM:MeOH (97:3)):ammonia (100:0 increasing in polarity to 99:1)

[10] Purified by Isolute amine column

[11] Recrystallised from MeOH

[12] Starting amine - Method 58

[13] Starting amine - Method 59

[14] Starting amine - JACS 1950, 72, 3539

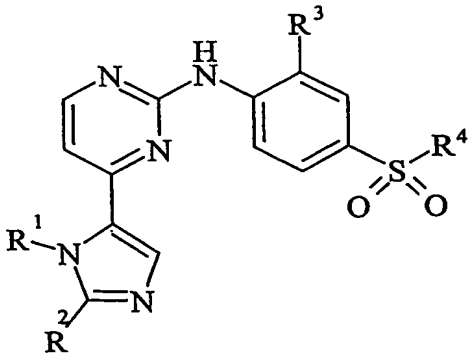
Example 15

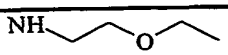
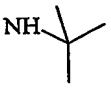
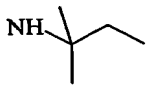
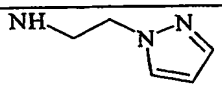
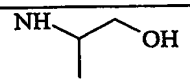
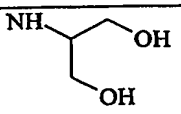
4-(1-Ethylimidazol-5-yl)-2-{4-[*N*-(cyclopropyl)sulphamoyl]anilino}pyrimidine

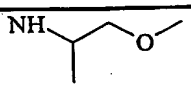
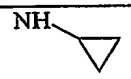
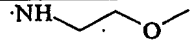
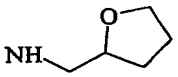
Chlorosulphonic acid (250µl, 3.6mmol) was added dropwise to solution of 2-anilino-4-(1-ethylimidazol-5-yl)pyrimidine (Method 19; 250mg, 0.9mmol) in thionyl chloride (5ml) cooled at 0°C and the mixture stirred at 0°C for 10 minutes then heated at 90°C for 90 minutes. The volatiles were removed by evaporation and the residue was dried under high vacuum (<2mmHg) for 1 hour. The resulting solid was placed under nitrogen and a solution of cyclopropylamine (1ml, 13.5mmol) in MeOH (4ml) added. The mixture was stirred for 15 minutes and the volatiles were evaporated in vacuo. Water (20ml) was added and the resultant solid was washed with water (2 x 10ml), ether (2 x 10ml) and dried under vacuum at 60°C for 18hr. The resultant solid was dissolved in MeOH (4ml) and treated with 1M HCl in ether (0.62ml, 0.62mmol). The solvent was evaporated in vacuo and the resultant solid triturated with ether, collected by filtration and dried under vacuum at 60°C to yield the title compound (220mg, 56%) as a golden solid. NMR: 0.34 (m, 2H), 0.52 (m, 2H), 1.52 (t, 3H), 2.21 (m, 1H), 4.77 (q, 2H), 7.43 (d, 1H), 7.74 (m, 3H), 7.93 (d, 2H), 8.54 (s, 1H), 8.72 (d, 1H), 9.41 (s, 1H), 10.20 (brs, 1H); m/z 385.

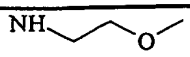
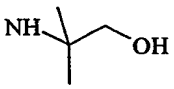
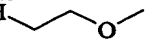
Examples 16-32

The following compounds were prepared by the procedure of Example 15 using the appropriate starting materials.



Ex	R^1	R^2	R^3	R^4	NMR	M/z	SM
16 1	Me	Me	H		1.04 (t, 3H), 2.40 (s, 3H), 2.88 (q, 2H), 3.32 (m, 4H), 3.96 (s, 3H), 7.18 (d, H), 7.44 (t, 1H), 7.68 (s, 1H), 7.70 (d, 2H), 7.92 (d, 2H), 8.44 (d, 1H), 9.92 (s, 1H)	417	Meth 21
17 1	Me	Me	H		1.15 (s, 9H), 2.38 (s, 3H), 3.97 (s, 3H), 7.19 (d, 1H), 7.24 (s, 1H), 7.63 (s, 1H), 7.76 (d, 2H), 7.88 (d, 2H), 8.42 (d, 1H), 9.87 (s, 1H)	401	Meth 21
18 1,2	Me	Me	H		0.74 (t, 3H), 1.05 (s, 3H), 1.45 (q, 2H), 2.40 (s, 3H), 3.95 (s, 3H), 7.22-7.18 (m, 2H), 7.65 (s, 1H), 7.70 (d, 2H), 7.91 (d, 2H), 8.45 (d, 1H), 9.90 (s, 1H)	415	Meth 21
19 1	Me	Me	H		2.39 (s, 3H), 3.12 (q, 2H), 3.96 (s, 3H), 4.15 (t, 2H), 6.19 (s, 1H), 7.20 (d, 1H), 7.40 (s, 1H), 7.58 (t, 1H), 7.68-7.62 (m, 4H), 7.92 (d, 2H), 8.43 (d, 1H), 9.92 (s, 1H)	439	Meth 21
20 1	Me	Me	H		0.89 (d, 3H), 2.40 (s, 3H), 3.08 (t, 2H), 3.96 (s, 3H), 4.60 (s, 1H), 7.22 (dd, 2H), 7.74 (m, 3H), 7.92 (d, 2H), 8.43 (d, 1H), 9.90 (s, 1H)		Meth 21
21 1,3	Me	Me	H		2.39 (s, 3H), 3.08-3.00 (m, 2H), 3.32-3.22 (m, 2H), 3.60-3.44 (m, 1H), 3.98 (s, 3H), 4.50 (t, 2H), 7.14 (d, 1H), 7.20 (d, 1H), 7.64 (s, 1H), 7.73 (d, 2H), 7.90 (d, 2H), 8.44 (d, 1H), 9.89 (s, 1H)	419	Meth 21

221	Me	Me	H		0.9 (d, 3H), 2.38 (s, 3H), 3.25-3.06 (m, 6H), 3.97 (s, 3H), 7.20 (d, 1H), 7.40 (d, 1H), 7.64 (s, 1H), 7.72 (d, 2H), 7.92 (d, 2H), 8.43 (d, 1H), 9.89 (s, 1H)	417	Meth 21
23	*i*-Pr	H	H		0.34 (m, 2H), 0.52 (m, 2H), 1.52 (d, 6H), 2.21 (m, 1H), 5.81 (m, 1H), 7.43 (d, 1H), 7.74 (m, 3H), 7.92 (d, 2H), 8.52 (s, 1H), 8.71 (d, 1H), 9.54 (s, 1H), 10.20 (brs, 1H)	399	Meth 20
24	*i*-Pr	H	H		1.52 (d, 6H), 2.86 (m, 2H), 3.16 (s, 3H), 3.28 (m, 2H), 5.79 (m, 1H), 7.38 (d, 1H), 7.55 (m, 1H), 7.72 (d, 2H), 7.86 (d, 2H), 8.52 (s, 1H), 8.68 (d, 1H), 9.58 (s, 1H), 10.20 (brs, 1H)	417	Meth 20
25	*i*-Pr	H	H		1.50 (m, 7H), 1.75 (m, 3H), 2.86 (m, 2H), 3.55 (m, 1H), 3.66 (m, 1H), 3.78 (m, 1H), 5.80 (m, 1H), 7.38 (d, 1H), 7.53 (m, 1H), 7.72 (d, 2H), 7.86 (d, 2H), 8.52 (s, 1H), 8.68 (d, 1H), 9.58 (s, 1H), 10.19 (brs, 1H)	443	Meth 20
264	*i*-Pr	Me	H		1.52 (d, 6H), 2.39 (s, 3H), 3.18 (s, 3H), 2.79 (s, 3H), 5.58 (m, 1H), 7.28 (d, 1H), 7.30 (br t, 1H), 7.69 (d, 2H), 7.89 (d, 2H), 8.20 (s, 1H) 8.70 (d, 1H), 10.20 (s, 1H), 15.00 (v brs, 0.7H)	387	Meth 18

27[5]	Et	H	H		1.40 (t, 3H), 2.90 (q, 2H), 3.15 (s, 3H), 3.3 (t, 2H), 4.75 (q, 2H), 7.4 (d, 1H), 7.5 (t, 1H), 7.73 (d, 2H), 7.9 (d, 2H), 8.5 (s, 1H), 8.7 (d, 1H), 9.30 (s, 1H)	403	Meth 19
28[1,6]	Me	Me	H		1.00 (s, 6H), 2.37 (s, 3H), 3.17 (d, 2H), 3.95 (s, 3H), 4.68 (t, 1H), 7.0 (s, 1H), 7.17 (d, 1H), 7.63 (s, 1H), 7.73 (d, 2H), 7.87 (d, 2H), 8.43 (d, 1H), 9.87 (s, 1H)	417	Meth 21
29[1]	Me	Me	F		2.37 (s, 3H), 2.93 (t, 2H), 3.17 (s, 3H), 3.28 (t, 2H), 3.84 (s, 3H), 7.2 (d, 1H), 7.6 (m, 3H), 7.67 (s, 1H), 8.08 (t, 1H), 8.38 (d, 1H), 9.4 (s, 1H)	421	Meth 22
30[1,5]	Me	Me	F	NH_2	2.35 (s, 3H), 3.85 (s, 3H), 7.2 (d, 1H), 7.35 (s, 2H), 7.62 (m, 3H), 8.07 (t, 1H), 8.4 (d, 1H), 9.35 (s, 1H)	363	Meth 22

[1] Isolated as free base

[2] Purified by flash silica chromatography DCM:MeOH (90:10)

[3] Purified by flash silica chromatography DCM:MeOH (85:15)

[4] Purified by flash silica chromatography DCM:MeOH (95:5 increasing in polarity to 90:10)

[5] Purified by Isolute amine column

[6] *i*-PrOH used in place of MeOH

Example 31

2-{4-[*N*-(1-Morpholino-2-methylprop-2-yl)sulphamoyl]anilino}-4-(1,2-dimethylimidazol-5-yl)pyrimidine

2-[4-(2,2-Dimethylaziridin-1-ylsulphonyl)anilino]-4-(1,2-dimethylimidazol-5-yl)pyrimidine (Example 50; 200mg, 0.502mmol) was dissolved on warming in morpholine (4.7ml, excess) and stirred at room temperature for 3 days. The excess morpholine was

removed in vacuo and the residue dissolved in EtOAc (40ml) and washed with water (3 x 40ml), dried the solvent evaporated in vacuo. The crude product was triturated with ether filtered washed with ether and air-dried to give the title compound (200mg, 82%) as a white solid. NMR 1.03 (s, 6H), 2.27 (s, 2H), 2.38 (s, 3H), 2.47 (m, 4H), 3.52 (m, 4H), 3.95 (s, 3H), 7.05 (s, 1H), 7.2 (d, 1H), 7.63 (s, 1H), 7.72 (d, 2H), 7.88 (d, 2H), 8.43 (d, 1H), 9.86 (s, 1H); m/z 486.

Example 32

Example 32 was prepared by the procedure of Example 31 using the appropriate starting material

Ex	Compound	NMR	m/z
32	2-{4-[*N*-(1-Pyrrolidin-1-yl-2-methylprop-2-yl)sulphamoyl] anilino}-4-(1,2-dimethylimidazol-5-yl)pyrimidine	1.03 (s, 6H), 1.62 (m, 4H), 2.35 (s, 3H), 2.42 (s, 2H), 2.53 (m, 4H), 3.93 (s, 3H), 6.95 (s, 1H), 7.18 (d, 1H), 7.63 (s, 1H), 7.73 (d, 2H), 7.87 (d, 2H), 8.43 (d, 1H), 9.86 (s, 1H)	470

Example 33

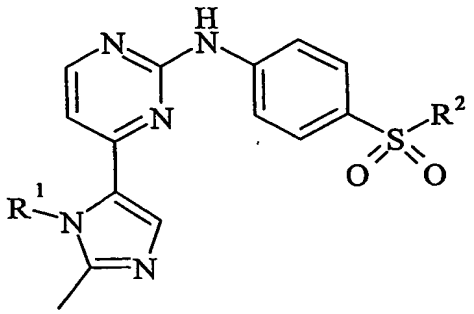
4-(1-Isopropyl-2-methylimidazol-5-yl)-2-{4-[*N*-(2-ethoxyethyl)sulphamoyl]anilino} pyrimidine

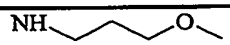
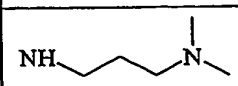
To a stirred solution of 2-amino-4-(1-isopropyl-2-methylimidazol-5-yl)pyrimidine (Method 23; 163mg, 0.75mmol), *N*-(2-ethoxyethyl)-4-iodobenzenesulphonamide (Method 28; 400mg, 1.13 mmol), tris(dibenzylideneacetone) dipalladium (0) (35mg, 0.038mmol) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (47mg, 0.076mmol) in dioxane (10ml) was added sodium *t*-butoxide (258mg, 2.69mmol) and the mixture heated at 80°C overnight. The reaction was cooled to room temperature and MeOH 105ml) was added and the mixture poured onto an Isolute SCX-2 column, eluted first with MeOH (10 x 30ml) and the product was then eluted with 5% methanolic ammonia (10 x 30ml). The solvent was removed by evaporation and the residue purified by flash chromatography on silica gel eluting with DCM/ MeOH (100:0 increasing in polarity to 97:3) to yield a foam which was dissolved in MeOH (2ml) and treated with 1N HCl in ether (350µl, 0.35mmol) for 5 minutes. Solvent was evaporated in vacuo to yield a yellow foam which was triturated with ether to yield after filtration the title

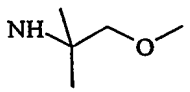
compound as a yellow solid (141mg, 39%) NMR: 1.05 (t, 3H), 1.53 (d, 6H), 2.80 (s, 3H), 2.85 (q, 2H), 3.32 (m, 4H), 5.58 (m, 1H), 7.21 (d, 1H), 7.52 (t, 1H), 7.73 (d, 2H), 7.86 (d, 2H), 8.39 (s, 1H), 8.68 (d, 1H), 10.18 (brs, 1H); m/z 445.

Examples 34-39

The following compounds were prepared by the procedure of Example 33 using the appropriate starting materials.



Ex	R^1	R^2	NMR	M/z	SM
342	*i*-Pr		1.57 (d, 6H), 1.78 (m, 2H), 2.81 (s, 3H), 3.18 (s, 3H), 3.28 (m, 2H), 3.36 (m, 2H), 5.58 (m, 1H), 7.30 (d, 1H), 7.82 (d, 2H), 7.99 (d, 2H), 8.22 (s, 1H), 8.78 (d, 1H), 10.32 (s, 1H),	434	Meth 23 Meth 49
353	*i*-Pr	Me	1.52 (d, 6H), 2.79 (s, 3H), 3.14 (s, 3H), 5.56 (m, 1H), 7.28 (d, 1H), 7.83 (d, 2H), 7.96 (d, 2H), 8.20 (s, 1H), 8.71 (d, 1H), 10.28 (s, 1H),	372	Meth 23
364	*i*-Pr		1.52 (d, 6H), 1.98 (m, 2H), 2.68 (s, 9H), 3.09 (t, 2H), 3.38 (t, 2H), 5.58 (m, 1H), 7.25 (d, 1H), 7.81 (d, 2H), 7.98 (s, 1H), 7.99 (d, 2H), 8.65 (d, 1H), 10.25 (s, 1H), 10.53 (brs, 0.7H)	443	Meth 23 Meth 45
375	*i*-Pr	*n*-Bu	0.82 (t, 3H), 1.30 (m, 2H), 1.49 (m, 2H), 1.51 (d, 6H), 2.80 (s, 3H), 3.22 (m, 2H), 5.54 (m, 1H), 7.29 (d, 1H), 7.79 (d, 2H), 7.96 (d, 2H), 8.20 (s, 1H), 8.71 (d, 1H), 10.29 (s, 1H), 15.10 (v brs, 0.7H)	414	Meth 23 Meth 47

38[6]	*i*-Pr	CF_3-$(CH_2)_2$-	1.52 (d, 6H), 2.58 (m, 2H), 2.80 (s, 3H), 3.55 (m, 2H), 5.56 (m, 1H), 7.30 (d, 1H), 7.89 (d, 2H), 8.00 (d, 2H), 8.22 (s, 1H), 8.76 (d, 1H), 10.36 (s, 1H), 15. 50 (v brs, 0.7H)	454	Meth 23 Meth 46
39[1]	Me		1.05 (s, 6H), 2.37 (s, 3H), 3.1 (s, 5H), 3.95 (s, 3H), 7.18 (d, 1H), 7.22 (s, 1H), 7.63 (s, 1H), 7.76 (d, 2H), 7.88 (d, 2H), 8.43 (d, 1H), 9.86 (s, 1H)	431	Meth 24 Meth 27

[1] Isolated as free base

[2] Purified by flash silica chromatography (DCM:MeOH 98:2):ammonia (100:0 increasing in polarity to 99:1) Residues was further purified by flash silica chromatography DCM:MeOH (96:4)

[3] Purified by flash silica chromatography DCM:MeOH (98:2 increasing in polarity to 90:10)

[4] Purified by flash silica chromatography DCM:MeOH/NH_3 (1%v/v) (95:5 increasing in polarity to 85:15)

[5] Purified by flash silica chromatography DCM:MeOH (97:3 increasing in polarity to 95:5)

[6] Purified by flash silica chromatography DCM:MeOH (95:5)

Example 40

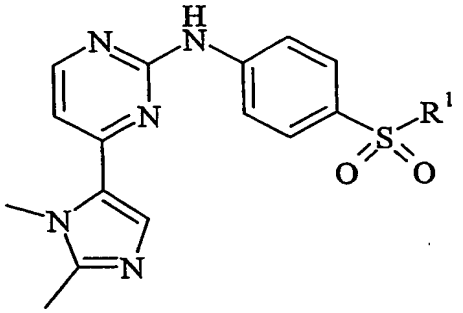
4-(1,2-dimethylimidazol-5-yl)-2-{4-[*N*-(1,3-dimethoxyprop-2-yl)sulphamoyl]anilino} pyrimidine

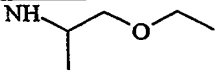
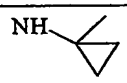
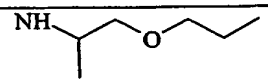
Chlorosulphonic acid (230µl, 3.31 mmol) was added to a solution of the 2-anilino-4-(1,2-dimethylimidazol-5-yl)pyrimidine (Method 21; 300mg, 1.12mmol) in thionyl chloride (6ml) at 5°C. The mixture was stirred at 5°C for 30 minutes, room temperature for 1 hour and heated at reflux for 1.5 hour. The mixture was allowed to cool to room temperature and a solution of excess 1,3-dimethoxy-2-aminopropane (Method 39) in ethanol (20ml) and dimethylethylamine (0.5ml) were added to the residue, and the mixture stirred at room temperature for 18 hours. The volatiles were removed by evaporation. The residue was triturated with water and the solid product collected by filtration and dried under vacuum at 60°C . The residue was purified by flash silica chromatography DCM:MeOH (95:5) to give the title compound. NMR: 2.40 (s, 3H), 3.10 (s, 6H), 3.20 (d, 4H), 3.32-3.28 (m, 1H), 3.98 (s,

3H), 7.20 (d, 1H), 7.55 (d, 1H), 7.65 (s, 2H), 7.74 (d, 2H), 7.90 (d, 2H), 8.44 (d, 2H), 9.89 (s, 1H); m/z 447

Examples 41-43

The following compounds were prepared by the procedure of Example 40 using the appropriate amine.



Ex	R^1	NMR	M/z
41 [2]		0.9 (d, 3H), 1.0 (t, 3H), 2.38 (s, 3H), 3.14-3.08 (m, 1H), 3.31-3.20 (m, 4H), 3.97 (s, 3H), 7.19 (d, 1H), 7.38 (d, 1H), 7.63 (s, 1H), 7.7 (d, 2H), 7.90 (d, 2H), 8.43 (d, 1H), 9.91 (s, 1H)	431
42 [3,1]		0.02 (t, 2H), 0.25 (t, 2H), 0.75 (s, 3H), 2.08 (s, 3H), 3.64 (s, 3H), 6.90 (d, 2H), 7.31 (s, 1H), 7.38 (d, 2H), 7.45 (s, 1H), 7.60 (d, 2H), 8.10 (d, 1H), 9.60 (s, 1H)	399
43 [4]		0.79 (t, 3H), 0.89 (d, 3H), 1.40 (q, 2H), 2.39 (s, 3H), 3.12-3.08 (m, 1H), 3.23-3.18 (m, 4H), 3.96 (s, 3H), 7.20 (d, 2H), 7.40 (d, 1H), 7.64 (s, 1H), 7.75 (d, 2H), 7.92 (d, 2H), 8.41 (d, 1H), 9.90 (s, 1H)	445

[1] Starting Material : Method 32

[2] Purified by flash silica chromatography DCM:MeOH (96:4)

[3] Purified by flash silica chromatography DCM:MeOH (93:7)

[4] Purified by flash silica chromatography DCM:MeOH (97:3)

Example 44

2-{4-[*N*-(1-Methylthio-2-methylprop-2-yl)sulphamoyl]anilino}-4-(1,2-dimethylimidazol-5-yl)pyrimidine

2-[4-(2,2-Dimethylaziridin-1-ylsulphonyl)anilino]-4-(1,2-dimethylimidazol-5-yl)pyrimidine (Example 50; (200mg, 0.50mmol) was dissolved in dry DMF (10ml) and NaSMe (176mg, 2.51mmol) added as a solid. The mixture was stirred under inert gas at room temperature overnight. Acetic acid (150µl, 2.62mmol) was added and volatiles were evaporated vacuo. The residue was treated with EtOAc (30ml)/water (30ml) and the suspension filtered and the solid washed with water and dried. The crude product was triturated with MeOH, filtered, washed with MeOH and dried to give the title compound (205mg, 75%) as a white solid; NMR 1.10 (s, 6H), 2.06 (s, 3H), 2.37 (s, 3H), 2.62 (2, 2H), 3.95 (s, 3H), 7.2 (d, 1H), 7.35 (s, 1H), 7.63 (s, 1H), 7.73 (d, 2H), 7.87 (d, 2H), 8.43 (d, 1H), 9.86 (s, 1H), m/z 447.

Example 45

The following compound was prepared by the procedure of Method 53 using Method 52 as a starting material.

Ex	Compound	NMR	m/z
45	5-Bromo-4-(1-isopropyl-2-methylimidazol-5-yl)-2-{4-[*N*-(2-methoxyethyl)sulphamoyl]anilino}pyrimidine	1.44 (d, 6H), 2.78 (s, 3H), 2.87 (q, 2H), 3.15 (s, 3H), 3.28 (t, 2H), 5.76 (m, 1H), 7.59 (t, 1H), 7.71 (d, 2H), 7.87 (d, 2H), 8.01 (s, 1H), 8.96 (s, 1H), 10.52 (s, 1H), 14.50 (v brs, 0.7H)	509

Example 46

5-Cyano-4-(1-ethyl-2-methylimidazol-5-yl)-2-{4-[*N*-(2-methoxyethyl)sulphamoyl]anilino}pyrimidine

A suspension of 5-bromo-4-(1-ethyl-2-methylimidazol-5-yl)-2-{4-[*N*-(2-methoxyethyl) sulphamoyl]anilino}pyrimidine (Method 60; 0.35g, 0.70mmol), zinc cyanide (0.05g, 0.42mmol), tris(dibenzylideneacetone)dipalladium(0) (0.02g, 0.02mmol) and 1,1'-bis(diphenylphosphino)ferrocene (0.03g, 0.05mmol) in DMF (7ml, 0.1M) was degassed (N_2 purge), then heated at 120°C for 48h. The mixture was cooled and filtered through diatomaceous earth, then concentrated in vacuo and the residue was purified by flash silica

chromatography DCM:MeOH (97:3) to give the title compound as a yellow oil (80mg, 26%). NMR 1.22 (t, 3H), 2.52 (s, 3H), 3.15 (q, 2H), 3.27 (s, 3H), 3.42 (t, 2H), 4.41 (q, 2H), 5.08 (t, 1H), 7.75 (d, 1H), 7.83 (d, 1H), 7.90 (s, 1H), 8.18 (s, 1H), 8.68 (s, 1H); m/z 442.

Example 47

2-[4-(2,2-Dimethylaziridin-1-ylsulphonyl)anilino]-4-(1,2-dimethylimidazol-5-yl)pyrimidine

To a solution of 2-{4-[N-(1-(4-toluenesulphonyloxy)-2-methylprop-2-yl)sulphamoyl] anilino}-4-(1,2-dimethylimidazol-5-yl)pyrimidine (Method 61; 2.14g, 3.75mmol) in acetone (73ml) was added powdered anhydrous potassium carbonate (0.57g, 4.13mmol). The mixture was heated at reflux for 4 hours. The reaction mixture was allowed to cool filtered and the solid washed with acetone. The filtrate was evaporated to give the title compound (1.36g, 91%) as a white solid. NMR 1.42 (s, 6H), 2.37 (s, 3H), 2.43 (s, 2H), 3.95 (s, 3H), 7.20 (d, 1H), 7.63 (s, 1H), 7.77 (d, 2H), 7.95 (d, 2H), 8.43 (d, 1H), 10.0 (s, 1H), m/z 399.

Preparation of Starting Materials

The starting materials for the examples above are either commercially available or are readily prepared by standard methods from known materials. For example, the following reactions are an illustration, but not a limitation, of some of the starting materials used in the above reactions.

Methods 1-11

The following compounds were synthesised by the procedure as described in JOC 1987, 2714-2716.

Meth	Compound	NMR	m/z	SM
1	4-(Isopropylamino)-5-methylisoxazole	($CDCl_3$) 1.12 (d, 6H), 2.30 (s, 3H), 3.21 (1H, sept), 8.01 (s, 1H)	141	4-amino-5-methylisoxazole
2	5-Methyl-4-(N-isopropylacetamido)isoxazole	($CDCl_3$) 1.02 (brs, 6H), 1.80 (s, 3H), 2.38 (s, 3H), 4.99 (1H, sept), 8.09 (s, 1H)	183	Meth 1

3	5-Acetyl-1-isopropyl-2-methylimidazole	1.40 (d, 6H), 2.38 (s, 3H), 2.42 (s, 3H), 5.08 (brm, 1H), 7.81 (s, 1H)	167	Meth 2
4	5-Methyl-4-(N-acetamido)isoxazole	2.00 (s, 3H), 2.34 (s, 3H), 8.64 (s, 1H), 9.60 (brs, 1H)	141	4-amino-5-methylisoxazole hydrochloride
5	5-Methyl-4-(ethylamino)isoxazole hydrochloride	1.21 (t, 3H), 2.58 (s, 3H), 3.22 (q, 2H), 8. 76 (s, 1H)	127	Meth 4
6	5-Methyl-4-(N-ethylacetamido)isoxazole	0.96 (t, 3H), 1.77 (s, 3H), 2.36 (s, 3H), 3.52 (q, 2H), 8.70 (s, 1H)	169	Meth 5
7	5-Acetyl-1-ethyl-2-methylimidazole	1.30 (t, 3H), 2.40 (m, 6H), 4.30 (q, 2H), 7.64 (s, 1H)	153	Meth 6
8	5-Methyl-4-(N-ethylformido)isoxazole	Used crude		Meth 5
9	5-Acetyl-1-ethylimidazole	1.23 (t, 3H), 2.48 (s, 3H), 4.27 (q, 2H), 7.86 (s, 1H), 7.92 (s, 1H)		Meth 8
10	5-Methyl-4-(N-isopropylformido)isoxazole	Used crude		Meth 1
11	5-Acetyl-1-isopropylimidazole	1.38 (d, 6H), 2.48 (s, 3H), 5.13 (q, 2H), 7.86 (s, 1H), 8.10 (s, 1H)	153	Meth 10

Method 12

5-(3-Dimethylaminoprop-2-en-1-oyl)-1,2-dimethylimidazole

2-Methyl-4-acetylimidazole (Tetrahedron letters 1985, 26 (29), 3423-3426; 129g, 1.04mol) was dissolved in a mixture of DMF (900ml) and DMF.DMA (1.5l) and the mixture heated under reflux, under an atmosphere of nitrogen, for 18 hours. The reaction mixture was

allowed to cool to ambient temperature the product crystallised. The solid product was collected by filtration, washed with DMF.DMA and then ether and dried under vacuum at 40°C to give the title compound (115g, 57%) as a pale brown crystalline solid. NMR: 2.13 (s, 3H), 2.95 (s, 6H), 3.78 (s, 3H), 5.56 (d, 1H), 7.50 (d, 1H), 7.53 (s, 1H); m/z 194.

Methods 13-16

The following compounds were synthesised by the procedure of Method 12.

Meth	Compound	NMR	m/z	SM
13 [1]	5-(3-Dimethylaminoprop-2-en-1-oyl)-1-ethyl-2-methylimidazole	1.17 (t, 3H), 2.16 (s, 3H), 2.95 (s, 6H), 4.27 (q, 2H), 5.57 (d, 1H), 7.50 (d, 1H), 7.53 (s, 1H)	208	Meth 7
14 [2]	5-(3-Dimethylaminoprop-2-en-1-oyl)-1-isopropyl-2-methylimidazole	1.43 (d, 6H), 2.40 (s, 3H), 2.95 (brs, 6H), 3.31 (s, 3H), 5.22 (sept, 1H), 5.54 (d, 1H), 7.48 (s, 1H), 7.52 (d, 1H)	222	Meth 3
15	5-(3-Dimethylaminoprop-2-en-1-oyl)-1-ethylimidazole	1.23 (t, 3H), 2.95 (m, 6H), 4.31 (q, 2H), 5.60 (d, 1H), 7.55 (d, 1H), 7.62 (s, 1H), 7.76 (s, 1H)	194	Meth 9
16	5-(3-Dimethylaminoprop-2-en-1-oyl)-1-isopropylimidazole	1.43 (d, 6H), 2.95 (m, 6H), 5.32 (m, 1H), 5.58 (d, 1H), 7.60 (m, 2H), 7.90 (s, 1H)	ND	Meth 11

[1] Only DMF.DMA used as solvent

[2] Purified by flash chromatography on silica gel eluting with DCM/MeOH (98:2 increasing in polarity to 92.5:7.5)

Method 17

2-Anilino-4-(1-ethyl-2-methylimidazol-5-yl)pyrimidine

5-(3-Dimethylaminoprop-2-en-1-oyl)-1-ethyl-2-methylimidazole (Method 13; 2.10g, 10.1mmol), phenylguanidine hydrogen carbonate (2.2g, 11.1mmol) and sodium methoxide (1.2g, 22.2mmol) were suspended in anhydrous DMA (15ml) and the mixture heated at 110°C for 18 hours. The reaction mixture was allowed to cool to ambient temperature and poured into water (50ml). The solution was extracted EtOAc (2 x 50ml). The combined extracts were

washed with water (2 x 50ml) and then brine (2 x 50ml), dried and the volatiles removed by evaporation. The residue was triturated with ether, collected by filtration and air dried to give the title compound (1.48g, 53%) as a reddish brown solid. NMR 1.17 (t, 3H), 2.38 (s, 3H), 4.52 (q, 2H), 6.93 (t, 1H), 7.08 (d, 1H), 7.27 (t, 2H), 7.60 (s, 1H), 7.62 (d, 2H), 8.35 (d, 1H), 9.35 (s, 1H); m/z 280.

Methods 18-22

The following compounds were synthesised by the procedure of Method 17.

Ex	Compound	NMR	m/z	SM
18 [1]	2-Anilino-4-(1-isopropyl-2-methylimidazol-5-yl)pyrimidine	1.44 (d, 6H), 2.51 (s, 3H), 5.72 (septuplet, 1H), 6.99 (t, 1H), 7.04 (d, 1H), 7.30 (t, 2H), 7.42 (s, 1H), 7.67 (d, 2H), 8.39 (d, 1H), 9.42 (s, 1H)	294	Meth 14
19	2-Anilino-4-(1-ethylimidazol-5-yl)pyrimidine	1.21 (t, 3H), 4.55 (q, 2H), 6.96 (t, 1H), 7.16 (d, 1H), 7.29 (t, 2H), 7.62 (d, 2H), 7.70 (s, 1H), 7.86 (s, 1H), 8.38 (d, 1H), 9.40 (s, 1H)	266	Meth 15
20	2-Anilino-4-(1-isopropylimidazol-5-yl)pyrimidine	1.21 (d, 6H), 5.65 (m, 1H), 6.96 (t, 1H), 7.12 (d, 1H), 7.29 (t, 2H), 7.63 (m, 3H), 8.04 (s, 1H), 8.38 (d, 1H), 9.40 (s, 1H)	280	Meth 16
21 [2]	2-Anilino-4-(1,2-dimethylimidazol-5-yl)pyrimidine	2.37 (s, 3H), 3.93 (s, 3H), 6.95 (t, 1H), 7.08 (d, 1H), 7.28 (t, 2H), 7.59 (s, 1H), 7.69 (d, 2H), 8.35 (d, 1H), 9.43 (s, 1H)	266	Meth 12
22	2-(2-Fluoroanilino)-4-(1,2-dimethylimidazol-5-yl)pyrimidine	2.33 (s, 3H), 3.75 (s, 3H), 7.07 (d, 1H), 7.17 (m, 3H), 7.58 (s, 1H), 7.65 (t, 1H), 8.30 (d, 1H), 9.02 (s, 1H)	284	Meth 50

[1] Solid crystallised from EtOAc

[2] Recrystallized from MeOH

Method 23

2-Amino-4-(1-isopropyl-2-methylimidazol-5-yl)pyrimidine

5-(3-Dimethylaminoprop-2-en-1-oyl)-1-isopropyl-2-methylimidazole (Method 14; 4.9g, 22.2mmol) and guanidine hydrochloride (5.3g, 55.6mmol) were suspended in 1-butanol (70ml). NaOMe (4.8g, 88mmol) was added in one portion and the mixture heated under reflux, under an atmosphere of nitrogen, for 3 hours. The volatiles were removed by evaporation. Water (50ml) was added and extracted EtOAc (3 x 50ml). The organic layers were combined and dried evaporated in vacuo. The residue triturated with isohexane to give the title compound as a brown solid (1.9g, 40%). NMR: 1.46 (d, 6H), 2.43 (s, 3H), 5.45 (m, 1H), 6.50 (brs, 1H), 6.74 (d, 1H), 7.28 (s, 1H), 8.12 (d, 1H); m/z 218

Method 24

The following compounds were synthesised by the procedure of Method 23.

Ex	Compound	NMR	m/z	SM
24	2-Amino-4-(1,2-dimethylimidazol-5-yl)pyrimidine	2.16 (s, 3H), 3.93 (s, 3H), 6.52 (s, 2H), 6.80 (d, 1H), 7.47 (s, 1H), 8.17 (d, 1H)	190	Meth 24

Method 25

N-(1,1-Dimethyl-2-(4-iodosulphonyloxy)-ethyl)-4-iodosulphonamide

2-Amino-2-methyl-1-propanol (1.34g, 15mmol) was dissolved in dry pyridine and cooled to 0°C under inert gas. Pipsyl chloride (9.52g, 31.5mmol) was added in portions as a solid keeping temperature < 2°C. The stirred a further 10 minutes at 0°C and then at room temperature for 18hr. The reaction mixture was poured into vigorously stirred ice water and the pH adjusted to 1.0 using conc. HCl. The precipitated solid was filtered washed with water and dried to give the title compound (7.03g, 75%) as a brown solid; NMR ($CDCl_3$) 1.29 (s, 6H), 3.93 (s, 2H), 4.76 (s, 1H), 7.55 (m, 4H), 7.82 (d, 2H), 7.73 (d, 2H).

Method 26

2,2-Dimethylaziridin-1-yl-4-iodosulphonamide

To a stirred solution of *N*-(1,1-dimethyl-2-(4-iodosulphonyloxy)-ethyl)-4-iodosulphonamide (Method 25; 7.0g, 11.27mmol) in acetone (112ml) was added powdered anhydrous potassium carbonate (1.71g, 12.4mmol). The mixture was heated at reflux for 20 hours and left standing at room temperature for 2 days. The reaction mixture was filtered and the solid washed with acetone. The filtrate was evaporated in vacuo. The crude product was purified by flash silica chromatography DCM:isohexane (3:1) to give the title compound (3.36g, 88%) as a white solid. NMR ($CDCl_3$) 1.53 (s, 6H), 2.43 (s, 2 H), 7.63 (d, 2H), 7.85 (d, 2H); m/z 337.

Method 27

N-(1,1-Dimethyl-2-methoxyethyl)-4-iodosulphonamide

To a stirred solution of 2,2-dimethylaziridin-1-yl-4-iodosulphonamide (Method 26; 3.35g, 9.94mmol) in dry THF (100ml), under inert gas atmosphere was added rapidly NaOMe (2.68g, 49.7mmol. The suspension was heated at reflux under inert gas for 6 hours. The reaction mixture was allowed to cool and then poured onto a stirred mixture of distilled water and acetic acid (3.2ml, 22.4mmol). Ether (100ml) was added, washed with water (100ml), dried and the solvent evaporated in vacuo. The crude product was triturated with ether/isohexane, filtered, washed with i-hexane and dried to give the title compound (2.44g, 67%) as a white solid. NMR 1.03 (s, 6H), 3.07 (s, 3H), 3.1 (s, 2H), 7.55 (m, 3H), 7.93 (d, 2H); m/z 370.

Method 28

N-(2-Ethoxyethyl)-4-iodobenzenesulphonamide

2-Ethoxyethylamine (2.14g, 24mmol) and diisopropylethylamine (4.2ml, 24mmol) were dissolved in DCM (50ml) and cooled to 0°C. To this was added pipsyl chloride (6.05g, 20mmol) in portions and the reaction stirred for 18 hours. Volatiles were evaporated in vacuo. The residue was dissolved in EtOAc (50ml), washed with 0.33M citric acid (2 x 50ml), brine (50ml), dried and evaporated in vacuo to yield an oil which solidified on standing to give the title compound as a pale yellow solid (6.97g, 98%). NMR: 1.01 (t, 3H), 2.89 (q, 2H), 3.30 (m, 4H), 7.53 (~~d, 2H~~), 7.75 (~~t, 1H~~), 7.97 (d, 2H); m/z 354 $(M-H)^-$.

Method 29

2-(4-Cyanoanilino)-4-(1,2-dimethylimidazol-5-yl)pyrimidine

The title compound was prepared by the procedure of Example 33 using the appropriate starting material. NMR: 2.37 (s, 3H), 3.96 (s, 3H), 7.20 (d, 1H), 7.60 (s, 1H), 7.69 (d, 2H), 7.95 (d, 2H), 8.43 (d, 1H), 9.95 (brs, 1H); m/z 291.

Method 30

2-(4-Aminomethylanilino)-4-(1,2-dimethylimidazol-5-yl)pyrimidine

2-(4-Cyanoanilino)-4-(1,2-dimethylimidazol-5-yl)pyrimidine (Method 29; 1.48g, 5.1mmol) and 35%w/v aqueous ammonia (0.5ml, 26mmol)was dissolved in MeOH (150ml). Raney Ni (200mg) was added and the reaction was hydrogenated at 50°C and 50Bar for 18hr. Catalyst was removed by filtration and solvent evaporated in vacuo. Purified by Isolute SCX-2 Column MeOH: aq. NH_3 (polarity increasing from 99:1 to 92:8) to yield the title compound (630mg, 42%) as a solid. NMR 2.36 (s, 3H), 3.14 (s, 2H), 3.62 (s, 2H), 3.95 (s, 3H), 7.03 (d, 1H), 7.21 (d, 2H), 7.60 (m, 3H), 8.38 (d, 1H), 9.41 (s, 1H); m/z 295.

Method 31

1-(1-Methylcyclopropane)carboxamide

Oxalyl chloride (8.24ml, 0.095mol) and then DMF (few drops) were added to a solution of 1-(1-methylcyclopropane)carboxylic acid (9.42g, 0.094mol) in DCM (150ml) cooled at 5°C and the mixture stirred at 5°C for 30 minutes and then for 3 hours at ambient temperature. The solvent and excess oxalyl chloride were removed by evaporation, the residue dissolved in DCM and added to a solution of ammonia (excess) in MeOH cooled at 5°C. The mixture was allowed to warm to ambient temperature and the volatiles removed by evaporation to give the title compound. NMR: 0.29 (q, 2H), 0.71 (q, 2H), 1.02 (s, 3H), 6.62 (s, 1H), 6.85 (s, 1H).

Method 32

1-Amino-1-methylcyclopropane

Bromine (2.87ml, 0.056mol) was added to a solution of sodium hydroxide (13.5g, 0.338mol) in water (100ml) at 0-5°C. A slurry of 1-(1-methylcyclopropane)carboxamide (Method 31; 5.70g 0.056mol) in water (50ml) was then added and reaction mixture stirred at 5°C for 2 hours, then left to stand at ambient temperature for 24 hours. The mixture was then

heated at 80°C for 2.5 hours, allowed to cool and mixture distilled to give the title compound (bp 75-80°C). NMR: 0.2 (q, 2H), 0.14 (q, 2H), 0.96 (s, 3H), 1.42 (s, 2H).

Method 33

1,3-Dimethoxy-2-methanesulphonyloxypropane

To a solution of 1,3-dimethoxy-2-hydroxypropane (3.84g, 0.032mol) in DCM (70ml) cooled at 5°C was added triethylamine (5ml, 0.036mol) followed by slow addition of methanesulphonyl chloride (2.72ml, 0.035mol). The mixture was then stirred at ambient temperature for 24 hours. The mixture was then absorbed onto silica gel and purified by flash silica chromatography DCM:isohexane (3:1) to give the title compound (3.74g, 59%). NMR 3.15 (s, 3H), 3.28 (s, 6H), 3.52 (d, 4H), 4.78 (q, 1H).

Methods 34-35

The following compounds were prepared by the procedure of Method 33 using the appropriate starting materials.

Meth	Compound	NMR
34	1-Ethoxy-2-methanesulphonyloxypropane	1.10 (t, 3H), 1.28 (d, 3H), 3.14 (s, 3H), 3.42-3.48 (m, 2H), 3.65 (m, 2H), 4.78 (q, 1H)
35	1-Propoxy-2-methanesulphonyloxypropane	0.86 (t, 3H), 1.28 (d, 3H), 1.51 (q, 2H), 3.33-3.40 (m, 2H), 3.44 (d, 2H), 3.69 (d, 3H), 4.78 (q, 1H)

Method 36

1,3-Dimethoxy-2-azidopropane

1,3-Dimethoxy-2-methanesulphonyloxypropane (Method 33; 3.74g, 19mmol) and sodium azide (2.03g, 31mmol) in DMA (55ml) was heated at 100°C for 8 hours then left to stand at ambient temperature for 24 hours. The mixture was diluted with water, extracted with EtOAc, the extracts combined and washed with water, dried ($MgSO_4$) and the volatiles removed by evaporation to give the title compound (2.0g, 74%) as a clear oil.

Methods 37-38

The following compounds were prepared by the procedure of Method 36 using the appropriate starting materials.

Meth	Compound	SM
37	1-Ethoxy-2-azidopropane	Meth 34
38	1-propoxy-2-azidopropane	Meth 35

Method 39

1,3-Dimethoxy-2-aminopropane

10% Palladium on charcoal (500mg) was added to a solution of 1,3-dimethoxy-2-azidopropane (Method 36; 2g, 0.014mol) in ethanol (40ml) and the mixture stirred under an atmosphere of hydrogen at ambient temperature for 6 hours. The catalyst was removed by filtration through diatomaceous earth and the filter pad washed with ethanol to give a solution of the title compound in ethanol (20ml).

Methods 40-41

The following compounds were prepared by the procedure of Method 39 using the appropriate starting materials.

Meth	Compound	SM
40	1-Ethoxy-2-aminopropane	Meth 37
41	1-propoxy-2-aminopropane	Meth 38

Method 42

1-[3-(*N*,*N*-Dimethylamino)propylthio]-4-bromobenzene

3-(Dimethylamino)propyl chloride hydrochloride (3.48g, 22mmol) was added in portions to a suspension of 4-bromothiophenol (3.78g, 20mmol) and potassium carbonate (5.52g, 40mmol) in DMF (40ml) and the reaction mixture heated to 60°C for 15 minutes. The mixture was allowed to cool to ambient temperature and poured into water (100ml) and extracted with EtOAc (2 x 100ml). The extracts were combined, washed with brine (3 x 100ml), dried (Chemelut column 1010) and evaporated to give the title compound (5.25g, 96%) as a pale yellow oil. NMR 1.76 (m, 2H), 2.20 (s, 6H), 2.35 (t, 2H), 2.93 (t, 2H), 7.18 (d, 2H), 7.38 (d, 2H); m/z 276.

Method 43

1-(3,3,3-Trifluoropropylthio)-4-bromobenzene

3-Bromo-1,1,1-trifluoropropane (640µl, 6mmol) was added to a mixture of 4-bromothiophenol (945mg, 5mmol) and potassium carbonate (760mg, 5.5mmol) in DMF (5ml) and the reaction mixture heated at 40°C for 1 hour. The mixture was allowed to cool to ambient temperature and poured into water (50ml) and extracted with EtOAc (2 x 30ml). The extracts were combined, washed with brine (3 x 30ml), dried (Chemelut column 1010) and evaporated to give the title compound (1.36g, 95%) as a pale yellow oil. NMR 2.56 (m, 2H), 3.13 (t, 2H), 7.31 (d, 2H), 7.51 (d, 2H); m/z 285 (M^+).

Method 44

1-(1-Butylthio)-4-bromobenzene

The title compounds was synthesised in an analogous method to Method 43. NMR 0.85 (t, 3H), 1.38 (m, 2H), 1.51 (m, 2H), 2.96 (t, 2H), 7.23 (d, 2H), 7.46 (d, 2H); m/z 244 (M^+).

Method 45

1-[3-(*N,N*-Dimethylamino)propylsulphonyl]-4-bromobenzene

Oxone (14g, 23mmol) was added to a solution of 1-[3-(*N,N*-dimethylamino) propylthio]-4-bromobenzene (Method 42; 5.24g, 19.1mmol) in MeOH (150ml) and water (30ml) and the mixture was stirred at ambient temperature for 90 minutes. The reaction mixture was poured onto an Isolute SCX-2 column, washed MeOH (6 x 40ml) and the product eluted with 2% methanolic ammonia (10 x 40ml). The solvent was evaporated and residue purified by flash chromatography on silica gel eluting with DCM/ 2% methanolic ammonia (100:0 increasing in polarity to 94:6) to yield the title compound (4.68g, 80%) as a pale yellow oil. NMR 1.62 (m, 2H), 2.03 (s, 6H), 2.19 (t, 2H), 3.32 (m, 2H), 7.81 (m, 4H); m/z 306.

Method 46

1-(3,3,3-Trifluoropropylsulphonyl)-4-bromobenzene

Oxone (3.7g, 6mmol) was added to a solution of 1-(3,3,3-trifluoropropylthio)-4-bromobenzene (Method 43; 1.36, 4.75mmol) in MeOH (25ml) and water (5ml) and the mixture was stirred at ambient temperature for 18 hours. The MeOH evaporated and water (20ml) added and the mixture extracted with DCM. The extracts were dried (Chemelut column CE1005) and solvent removed by evaporation to give the title compound (1.43g, 95%) as a white solid. NMR 2.62 (m, 2H), 3.67 (m, 2H), 7.86 (s, 4H); m/z 316 (M^+).

Method 47

1-(1-Butylsulphonyl)-4-bromobenzene

The title compound was synthesised from Method 44 in an analogous method to Method 46. NMR: 0.80 (t, 3H), 1.31 (m, 2H), 1.47 (m, 2H), 3.29 (t, 2H), 7.78 (d, 2H), 7.86 (d, 2H); m/z 276 (M^+).

Method 48

3-Methoxy-1-propanol methanesulphonate

Methanesulphonyl chloride (1.75ml, 22mmol) was added to a solution of 3-methoxy-1-propanol (1.81g, 20mmol) and triethylamine (3.35ml, 24mmol) in DCM (40ml) cooled in an ice bath and the mixture stirred at ambient temperature for 18 hours. DCM (25ml) and water (50ml) were added and the phases separated and the aqueous layer was extracted with DCM (25ml). The extracts were combined, washed with water (50ml) and brine (50ml), dried (Chemelut column CE1010) and evaporated to give the title compound 3.25g (97%) as a pale yellow oil. NMR 2.00 (m, 2H), 3.01 (s, 3H), 3.35 (s, 3H), 3.49 (t, 2H), 4.38 (t, 2H).

Method 49

1-(3-Methoxypropylsulphonyl)-4-bromobenzene

Potassium carbonate (2.8g, 20mmol) was added to a solution of 3-methoxypropan-1-yl methansulphonate (Method 48; 3.25g, 19.3mmol) and 4-bromothiophenol (3.48g, 18.4mmol) in DMF (30ml) and the mixture heated at 40°C for 4 hours. The mixture was allowed to cool to ambient temperature, poured into water (100ml) and extracted with EtOAc (2 x 50ml). The extracts were combined, washed with saturated aqueous sodium hydrogen carbonate solution (50ml) and brine (2 x 50ml), dried (Chemelut column CE1010) and the volatiles removed by

evaporation. The residue was dissolved in MeOH (150ml) and water (30ml) and oxone (13.4g, 21.6mmol) was added in portions. The mixture was stirred at ambient temperature for 18 hours. The MeOH was evaporated, water (50ml) added and the solution extracted with DCM (3 x 50ml). The extracts were combined, washed with brine (50ml), dried (Chemelut column CE1010), and evaporated. The residue was purified by flash chromatography on silica gel eluting with iso-hexane : EtOAc (100:0 increasing in polarity to 90:10) to give the title compound (3.32g, 62%) as a colourless oil. NMR 1.95 (m, 2H), 3.19 (m, 2H), 3.26 (s, 3H), 3.41 (t, 2H), 7.70 (d, 2H), 7.78 (d, 2H).

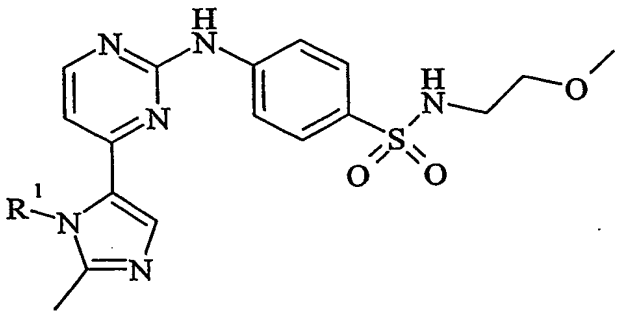
Method 50

2-Fluorophenylguanidine bicarbonate

Concentrated hydrochloric acid (6ml) in water (4.8ml) was added to a mixture of 2-fluoroaniline (7.94g, 71.2mmol) and cyanamide (6.98g, 166mmol) and the mixture heated at 115°C for 2.5 hours. The reaction mixture was allowed to cool to ambient temperature and the solution was adjusted to pH 13 by careful addition of 40% aqueous sodium hydroxide solution. The aqueous solution was extracted with EtOAc and the combined organic extracts were dried (Na_2SO_4) and the volatiles removed by evaporation. The crude product was dissolved in water (40 ml) and carbon dioxide gas bubbled through the solution until the pH of the suspension remained constant (approximately pH 9). The precipitated solid was collected by filtration, washed sparingly with water and dried to give the title compound (11.95g, 78%) as a white solid. NMR: 6.83 (m, 2H), 7.0 (m, 2H); m/z: 154.

Methods 51-52

The following compounds were prepared by the procedure of Example 15 using the appropriate starting materials.



Meth	R^1	NMR	M/z	SM
51 [1]	Et	1.25 (t, 3H), 2.40 (s, 3H), 3.05 (q, 2H), 3.20 (s, 3H), 3.36 (t, 2H), 4.43 (q, 2H), 4.92 (t, 1H), 6.95 (d, 1H), 7.32 (brs, 1H), 7.50 (s, 1H), 7.72 (m, 4H), 8.35 (d, 1H)	417	Meth 17
52 [1]	*i*-Pr	1.48 (d, 6H), 2.51 (s, 3H), 2.86 (m, 2H), 3.16 (s, 3H), 3.29 (t, 2H), 5.66 (septuplet, 1H), 7.14 (d, 1H), 7.46 (s, 1H), 7.49 (t, 1H), 7.69 (d, 2H), 7.89 (d, 2H), 8.45 (d, 1H), 9.88 (s, 1H)	431	Meth 18

Method 53

3-Hydroxyisoxazole

Hydroxylamine hydrochloride (35g, 0.5mol) was added to a solution of sodium hydroxide (58g, 1.45mol) in water (580ml). MeOH (600ml) followed by ethyl propiolate (38ml, 0.37mol) in portions was then added and the resulting solution stirred at ambient temperature for 6 days. The mixture was acidified to pH2 with concentrated hydrochloric acid and then saturated with sodium chloride. The solution was extracted with DCM (8 x 500ml), the extracts combined, dried and the solvent evaporated. The solid residue was washed with hot iso-hexane (3 x 300ml) and the final suspension was allowed to cool and the resulting solid was collected by filtration, dried under vacuum to give the title compound (11.16g, 35%) as a white solid crystallised. NMR 6.04 (s, 1H), 8.43 (s, 1H), 11.16 (s, 1H). m/z 85 (M^+).

Method 54

Ethynylcarbamoyl

To liquid ammonia (300ml) was added methyl propiolate (52.4g, 0.62mol) over 2 hours keeping the temperature at –70°C. The ammonia was left to evaporate and the reaction mixture evaporated *in vacuo* to yield the title compound (43g) which was used without any further purification. Mpt: 54-55°C.

Method 55

3-Oxo-2,3-dihydro-1,2,5-thiadiazole

To a stirred solution of ethynylcarbamoyl (Method 54; 43g, 0.62mol) in water (310ml) cooled in ice bath was added ammonium thiosulphate (92.35g, 0.62mol) in one portion. The reaction was allowed to warm to room temperature over 5 hours. To the reaction mixture was

added a solution of iodine (79.2g, 0.31mol) in MeOH (1l) rapidly over 10 minutes to yield a dark solution. Ammonium thiosuphate was added until a yellow solution was obtained. The solvent was evaporated to approximately 400ml and extracted ether (3 x 300ml). The ethereal solution was washed brine (100ml), passed through phase separation paper and evaporated *in vacuo* to yield the title compound as a pale orange solid (32.8g, 52%). Mpt: 70-71°C.

Method 56

3-[2-(*t*-Butoxycarbonylamino)ethoxy]-1,2,5-thiadiazole

Diisopropyl azodicarboxylate (1.1ml, 5.5mmol) was added dropwise to a solution of 2-(*t*-butoxycarbonylamino)ethanol (850µl, 5.5mmol), 3-oxo-2,3-dihydro-1,2,5-thiadiazole (Method 55; 510mg, 5mmol) and triphenylphosphine (1.44g, 5.5mmol) in THF (20ml) and the mixture was stirred at ambient temperature for 18 hours. The solvent was evaporated and the residue purified by flash chromatography on silica gel eluting with iso-hexane : EtOAc (100:0 increasing in polarity to 4:1) to give the title compound (1.17g, 95%) as a white solid. NMR 1.38 (s, 9H), 3.31 (m, 2H), 4.16 (t, 2H), 6.96 (m, 1H), 8.35 (s, 1H); m/z 246.

Method 57

The following compound was synthesised in an analogous method to Method 56 using the appropriate amine and heterocycle as starting materials.

Meth	Compound	NMR	m/z	SM
57	3-[3-(*t*-Butoxycarbonylamino) propoxy]isoxazole	1.36 (s, 9H), 1.80 (m, 2H), 3.04 (q, 2H), 4.17 (t, 2H), 6.24 (s, 1H), 6.83 (m, 1H), 8.61 (s, 1H)	243	Meth 53

Method 58

3-(2-Aminoethoxy)-1,2,5-thiadiazole hydrochloride

4M Hydrogen chloride in dioxane (10ml) was added to a solution of 3-[2-(*t*-butoxycarbonylamino)ethoxy]-1,2,5-thiadiazole (Method 56; 1.17g, 4.74mmol) in dioxane (20ml) and the mixture was stirred at ambient temperature for 2 days. The resulting solid was collected by filtration, washed with ether and dried to give the title compound (803mg, 93%) as a white solid NMR 3.20 (m, 2H), 4.58 (t, 2H), 8.36 (m, 4H); m/z 146.

Method 59

The following compound was synthesised in an analogous method to Method 58.

Meth	Compound	NMR	m/z	SM
59	3-(3-Aminopropoxy) isoxazole hydrochloride	2.02 (m, 2H), 2.83 (m, 2H), 4.24 (t, 2H), 6.29 (s, 1H), 8.20 (s, 3H), 8.61 (s, 1H)	143	Meth 57

Method 60

5-Bromo-4-(1-ethyl-2-methylimidazol-5-yl)-2-{4-[*N*-(2-methoxyethyl)sulphamoyl]anilino} pyrimidine

Bromine (8µl, 0.14mmol) was added to a solution of 4-(1-ethyl-2-methylimidazol-5-yl)-2-{4-[*N*-(2-methoxyethyl)sulphamoyl]anilino}pyrimidine (Method 51; 52mg, 0.13mmol) in glacial acetic acid (2ml) heated at 60°C The mixture was heated at 60°C for 4 hours, then the solvent was removed by evaporated. The residue was dissolved in DCM (20ml), washed with saturated aqueous sodium hydrogen carbonate solution (20ml), dried (Chemelut column 1005) and purified by flash chromatography eluting with DCM/ 2% methanolic ammonia (100:0 increasing in polarity to 97:3) to yield the title compound (37mg, 60%) as a white foam NMR 1.25 (t, 3H), 2.50 (s, 3H), 3.15 (q, 2H), 3.26 (s, 3H), 3.42 (t, 2H), 4.33 (q, 2H), 4.92 (t, 1H), 7.40 (s, 1H), 7.71 (d, 2H), 7.82 (m, 3H), 8.61 (s, 1H); m/z 497.

Method 61

2-{4-[*N*-(1-(4-Toluenesulphonyloxy)-2-methylprop-2-yl)sulphamoyl]anilino}-4-(1,2-dimethylimidazol-5-yl)pyrimidine

2-{4-[*N*-(1-Hydroxy-2-methylprop-2-yl)sulphamoyl]anilino}-4-(1,2-dimethylimidazol-5-yl)pyrimidine (Example 28; 2.36g, 5.66mmol) was dissolved in dry pyridine (55ml) and the solution stirred and cooled to 0°C under inert gas. Solid p-toluenesulphonyl chloride (5.61g, 29.4mmol) was added portionwise over 2 minutes. The reaction was stirred at 0°C for 10 minutes and then at room temperature for 18hr. The reaction mixture was diluted with water (200ml) and the precipitated oil allowed to settle out. The supernatant water layer was decanted off and the residual oil was washed with more water and this was decanted off. This process was repeated and then the oil partitioned between EtOAc (100ml) and water (50ml). The layers were separated and the organic layer washed with water (50ml), dried and the solvent evaporated in vacuo to yield the title compound as a gum (1.94g, 60%) NMR 1.0 (s,

6H), 2.36 (s, 3H), 2.38 (s, 3H), 3.77 (s, 2H), 3.93 (s, 3H), 7.20 (d, 1H), 7.43 (d, 2H), 7.55 (s, 1H), 7.65 (m, 5H), 7.87 (d, 2H), 8.45 (d, 1H), 9.9 (s, 1H); m/z 571.

Example 48

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof (hereafter compound X), for therapeutic or prophylactic use in humans:-

(a): Tablet I	**mg/tablet**
Compound X	100
Lactose Ph.Eur	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

(b): Tablet II	**mg/tablet**
Compound X	50
Lactose Ph.Eur	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0

(c): Tablet III	**mg/tablet**
Compound X	1.0
Lactose Ph.Eur	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

(d): Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur	488.5
Magnesium stearate	1.5

(e): Injection I	(50 mg/ml)
Compound X	5.0% w/v
1M Sodium hydroxide solution	15.0% v/v
0.1M Hydrochloric acid	(to adjust pH to 7.6)
Polyethylene glycol 400	4.5% w/v
Water for injection	to 100%

(f): Injection II	10 mg/ml
Compound X	1.0% w/v
Sodium phosphate BP	3.6% w/v
0.1M Sodium hydroxide solution	15.0% v/v
Water for injection	to 100%

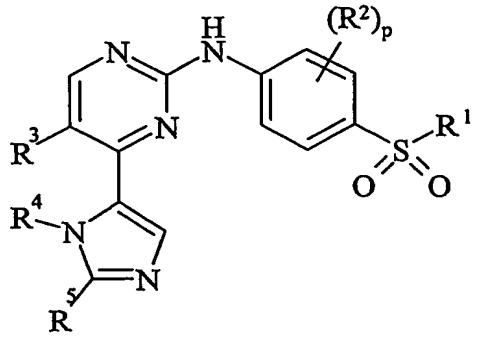
(g): Injection III	(1mg/ml,buffered to pH6)
Compound X	0.1% w/v
Sodium phosphate BP	2.26% w/v
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection	to 100%

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

Claims

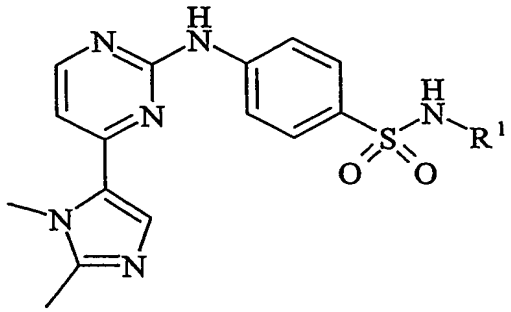
1. A compound of the formula **(IA)**, **(IB)**, **(IC)**, **(ID)**, **(IE)** and **(IF)** of the generic structure of formula **(I)**:



(I)

wherein:

i) a compound of formula **(IA)** is selected from:



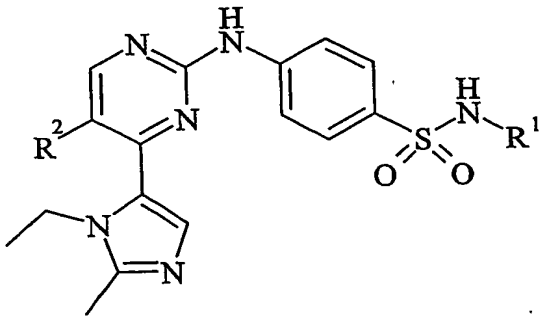
(IA)

wherein:

R^1 is 2-(pyrazolyl-1-yl)ethyl, 3-(isoxazol-3-yloxy)propyl, 2-(thiazol-3-yloxy)ethyl, 2-(thiadiazol-3-yloxy)ethyl, 1,3-dihydroxyprop-2-yl, 1-methyl-1-hydroxymethylethyl, 1,2-dimethylpropyl, 1-methylcyclopropyl, 2,2-dimethylaziridin-1-yl, *t*-butyl, 2-morpholino-1,1-dimethylethyl, 2-pyrrolidin-1-yl-1,1-dimethylethyl, 2-methylthio-1,1-dimethylethyl, 1,3-dimethoxyprop-2-yl, 1-methoxyprop-2-yl, 1-hydroxyprop-2-yl, 1-ethoxyprop-2-yl, 1-propoxyprop-2-yl, ethoxyethyl or 2-methoxy-1,1-dimethylethyl;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof;

ii) a compound of formula **(IB)** is selected from:



(IB)

wherein:

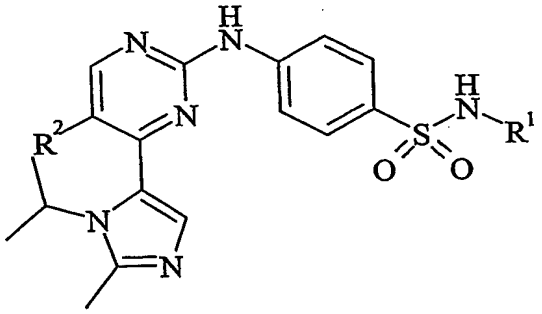
R^1 is pyrid-2-ylmethyl, 2-(2-methyl-1,2,4-triazol-5-yl)ethyl, 2-pyrid-2-ylethyl, 2-pyridazin-3-ylethyl, 2-(3,5-dimethyltriazol-4-yl)ethyl, 2-pyrid-3-ylethyl, 2-methoxyethyl, 3-(5-methylpyrazol4-yl)propyl, 2-trifluoromethylpyrid-5-ylmethyl, 2-pyridazin-4-ylethyl, 1,1-dimethylpropyn-2-yl or 2-ethoxyethyl; and

R^2 is hydrogen or cyano;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof;

provided that when R^1 is 2-methoxyethyl, R^2 is cyano;

iii) a compound of formula **(IC)** is selected from:



(IC)

wherein:

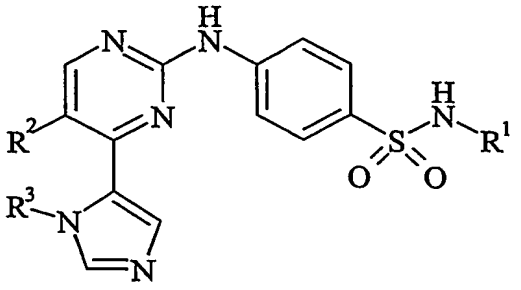
R^1 is hydrogen, C_{1-6}alkyl or C_{1-6}alkoxyC_{1-6}alkyl; and

R^2 is hydrogen, halo or cyano;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof;

provided that when R^1 is 2-methoxyethyl, R^2 is not hydrogen;

iv) a compound of formula **(ID)** is selected from:



(ID)

wherein:

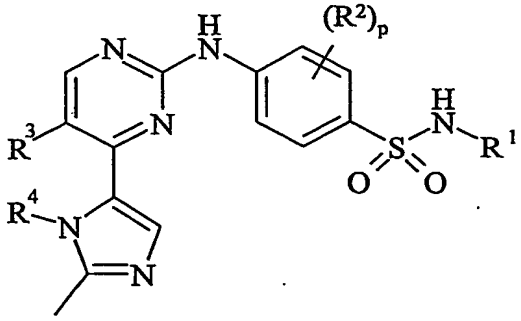
$\mathbf{R^1}$ is hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, a heterocyclyl or heterocyclylC_{1-3}alkyl; wherein R^1 may be optionally substituted on carbon by one or more methyl, ethyl, methoxy, ethoxy, propoxy, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy or cyclopropylmethoxy; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by one or more methyl, ethyl, acetyl, 2,2,2-trifluoroethyl or methoxyethyl;

$\mathbf{R^2}$ is hydrogen, halo or cyano;

$\mathbf{R^3}$ is C_{2-6}alkyl;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof;

v) a compound of formula **(IE)** is selected from:



(IE)

wherein:

$\mathbf{R^1}$ is hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, a heterocyclyl or heterocyclylC_{1-3}alkyl; wherein R^1 may be optionally substituted on carbon by one or more methyl, ethyl, methoxy, ethoxy, propoxy, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy or cyclopropylmethoxy; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by one or more methyl, ethyl, acetyl, 2,2,2-trifluoroethyl or methoxyethyl;

R^2 is halo, cyano, C_{1-3}alkyl or C_{1-3}alkoxy;

p is 1-2; wherein the values of R^2 may be the same or different;

R^3 is hydrogen, halo or cyano;

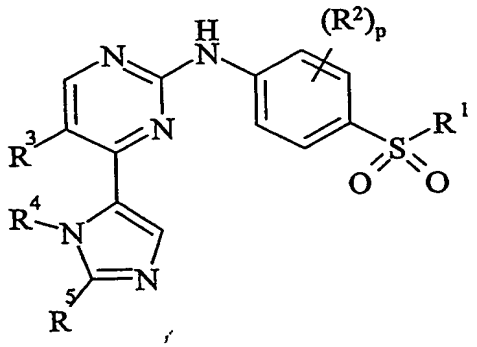
R^4 is C_{1-4}alkyl;

R^5 is C_{1-6}alkyl or C_{2-6}alkenyl; wherein R^5 may be optionally substituted on carbon by one or more methoxy, ethoxy, propoxy, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy or cyclopropylmethoxy;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof;

provided that said compound is not 4-(1,2-dimethylimidazol-5-yl)-2-[2-methoxy-4-(*N*-methylsulphamoyl)-5-methylanilino]pyrimidine; and

vi) a compound of formula **(IF)** is selected from:



(IF)

wherein:

R^1 is C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, a heterocyclyl or heterocyclylC_{1-3}alkyl; wherein R^1 may be optionally substituted on carbon by one or more methyl, ethyl, methoxy, ethoxy, propoxy, trifluoromethyl, trifluoromethoxy, dimethylamino, 2,2,2-trifluoroethoxy or cyclopropylmethoxy; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by one or more methyl, ethyl, acetyl, 2,2,2-trifluoroethyl or methoxyethyl;

R^2 is halo, cyano, C_{1-3}alkyl or C_{1-3}alkoxy;

p is 0-2; wherein the values of R^2 may be the same or different;

R^3 is hydrogen, halo or cyano;

R^4 is C_{2-6}alkyl;

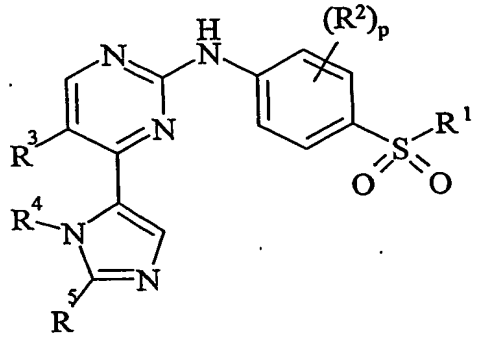
R^5 is C_{1-6}alkyl or C_{2-6}alkenyl; wherein R^5 may be optionally substituted on carbon by one or more methoxy, ethoxy, propoxy, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy or cyclopropylmethoxy;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

ABSTRACT

TITLE: CHEMICAL COMPOUNDS

Compounds of the formula (I):



(I)

wherein R^1, R^2, R^3, R^4, R^5 and p are as defined within and a pharmaceutically acceptable salts and *in vivo* hydrolysable esters are described. Also described are processes for their preparation and their use as medicaments, particularly medicaments for producing a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal, such as man.